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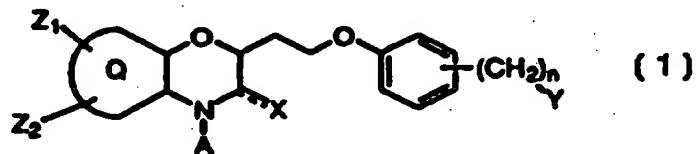
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(71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; U.S. Route 22 #202, Raritan, NJ 08869-0602 (US).		
(72) Inventors: FRECHETTE, Roger, 150 County Line Road, Somerville, NJ 08876 (US). WEIDNER-WELLS, Michele, A.; 115 Reimer Street, Somerville, NJ 08876 (US).		
(74) Agents: CIAMPORCERO, Audley et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).		

(54) Title: BENZOXAZINE ANTIMICROBIAL AGENTS

(57) Abstract

The invention relates to benzoxazine and pyrido-oxazine antibacterial compounds of general formula (1), wherein the moiety Q is a fused phenyl or fused pyridyl moiety as herein described, pharmaceutical compositions containing the compounds, methods for their production and their use in treating bacterial infections.



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BENZOXAZINE ANTIMICROBIAL AGENTS

Field of the Invention

5 The invention relates to benzoxazine and pyrido-oxazine antibacterial compounds, pharmaceutical compositions containing the compounds, and methods for their production and use. These compounds are effective in inhibiting the action of a bacterial histidine protein kinase and are thus useful as anti-infective agents against a variety of bacterial
10 organisms, including organisms which are resistant to other known antibiotics.

Background of the Invention

15 Prokaryotes regulate the transcription of many of their genes in response to changes in the organisms' environment (J. B. Stock, A. M. Stock, and J. M. Mottonen, *Nature*, 344, 395-400 (1990)). Such regulation is essential if the organism is to adapt itself to survival in a changing environment, and pathogenic bacteria rely on such regulatory systems to enable them to survive within their host's body (J. F. Miller, J. J. Mekalanos, S. Falkow, *Science*, 243, 1059 (1989)). Chemical compounds that interfere with the regulatory mechanisms would be expected to be useful anti-infective drugs, as they would prevent bacteria from making necessary adaptive changes in their patterns of gene expression.

25 Virulence, chemotaxis, toxin production, sporulation, and reproduction are examples of the bacterial processes that are under regulatory control, and which could be inhibited by such compounds. The inhibition of one or more of these processes is expected to lead to reduced
30 virulence, a slowing or halting of bacterial growth and reproduction, and even to bacterial cell death if vital functions are interrupted.

For example, it has been shown that *Salmonella* species express certain proteins, under regulatory control and in response to the presence of
35 intestinal epithelial cells, which enable them to adhere to and invade these cells. Bacteria unable to synthesize these proteins are avirulent: they cannot cause infection in mice (B. B. Finlay, F. Heffron, S. Falkow, *Science*,

243, 940-943 (1989)). A similar effect would be expected if the genes coding for these proteins were intact, but remained unexpressed.

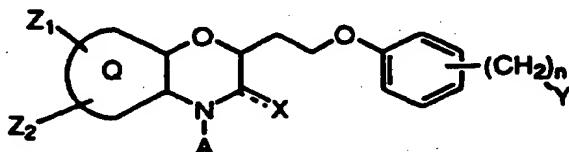
To accomplish adaptive responses to the environment, bacteria rely 5 on phosphorelay mechanisms, referred to in the art as "two-component switches." These switches have the net effect of transmitting information from the environment to the cell nucleus, where the information is responded to by the switching on or off of transcription of relevant genes. The first step of this phosphorelay scheme relies on numerous histidine 10 protein kinase (HPK) enzymes. Most of these HPK enzymes are sensor molecules, and respond to stimulation by specific environmental signals by transferring phosphate from ATP to a histidine residue of the HPK protein. Some HPK enzymes are stimulated by the presence of acceptor proteins 15 (described below), the concentration of which are modulated by environmental signals. In either case, this auto-phosphorylation is followed by transfer of the phosphate to an aspartyl residue of one or more acceptor proteins (the second components of the two-component switch), which are either regulators of gene expression (by binding to control regions on DNA, or to the RNA polymerase complex) or are themselves kinases for other 20 acceptor molecules. These secondary acceptors may again be regulatory proteins, or kinases toward yet another protein. This cascade of phosphate from protein to protein eventually results in the phosphorylation of one or more regulatory proteins, which then control gene expression.

25 Mammalian cells do not, or at least are not presently known to, utilize HPK-driven phosphorelay systems for gene regulation. Thus, compounds which selectively inhibit either the autophosphorylation of the HPK protein, or the phosphotransfer step(s), or both, would not be expected to have undesirable effects on the host organism, and are promising candidates for 30 antiinfective drugs. The emergence of drug-resistant pathogenic organisms that are resistant to one or more of the currently available drugs has created a need for novel antibiotics, that act by mechanisms unrelated to those of currently available agents, and inhibitors of HPK would fill this need. The presence of multiple HPK-driven systems (over fifty are currently known) in 35 bacteria gives HPK inhibitors a potential advantage over current antibiotics, in that mutations of a single HPK enzyme are unlikely to confer drug resistance to an organism.

Recently, workers in this field reported a method for detecting bacterial "virulence" genes that are selectively expressed when bacteria infect a host (M. J. Mahan, J. M. Slauch, and J. J. Mekalanos, *Science*, **259**, 686-688 (1993)). The potential use of this information in the design of new antibiotics was mentioned, but actual methods of reducing expression of these genes were not described. A preliminary report from another group of workers disclosed inhibitors of the two-component switch controlling alginate gene activation in *Pseudomonas aeruginosa* in an *in vitro* system (S. Roychoudhury *et al.*, *Proc. Nat. Acad. Sci.*, **90**, 965-969 (1993)), but no anti-bacterial activity of the compounds was reported.

Summary of the Invention

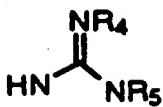
The invention comprises compounds of general structure 1 shown below:



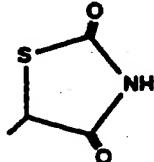
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Wherein the moiety Q is a fused phenyl or fused pyridyl moiety;
 20 Z_1 is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;
 Z_2 is hydrogen or a halogen;
 X is hydrogen or oxygen;
 A is C₁-C₆ alkyl, C₁-C₆ alkylaryl or C₁-C₆ alkylheterocyclyl
 25 wherein aryl is biphenyl, naphthyl or phenyl; and heterocyclyl is a 5 or 6 membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or a sulfur atom; .
 wherein said aryl or heterocyclyl group is optionally substituted with (C₁-C₆) alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C₁-C₄)alkoxy or methylsulfonylamino;
 30 n is an integer from 0-3;.
 Y is a moiety selected from:
 (a) NHR₁R₂, N⁺R₁R₂R₃;

(b)

(c) CO₂H, CHO;(d) CH(R₆)CO₂H, CH(R₆)CO₂CH₃, CH=CHR₇, CH=C(CO₂H)₂;

5 (e) a moiety of the formula:



(f) 5-tetrazolyl;

wherein

10 R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl, or t-butoxycarbonyl;R₄ and R₅ are independently t-butoxycarbonyl or hydrogen or R₄ and R₅ may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;15 R₆ is hydrogen, hydroxy or chloro;R₇ is CO₂H or C(O)NH(CH₂)_pOH wherein p is an integer from 1-4; and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

20 Another aspect of the invention comprises a method of treating bacterial infections in mammals by administering to a mammal suffering from such infection a therapeutically effective amount of a compound selected from those of Formula 1 effective in inhibiting the action of a bacterial histidine protein kinase.

25 The compounds of the present invention inhibit the autophosphorylation of bacterial histidine kinases; they also inhibit the transfer of phosphate from phosphorylated histidine kinases to the aspartyl residues of the phosphate acceptor proteins involved in regulation of 30 bacterial gene expression. The compounds of the present invention have been found to inhibit the growth of bacteria by the standard method, measurement of minimum inhibitory concentrations (MIC values). The compounds are useful as bacteriostatic and bactericidal agents, and as anti-

infective agents in the treatment of infectious diseases. They may also have utility in increasing the sensitivity of bacteria to conventional antibiotics.

Detailed Description

5 Relative to the above generic description, certain compounds of formula 1 are preferred.

Preferred embodiments are those compounds wherein Q is fused phenyl.

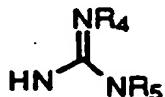
Preferred groups for A are C₁-C₅ alkyl, CH₂phenyl, CH₂thienyl,

10 CH₂pyridyl, CH₂furyl, or ethyl piperidine.

Preferred groups for Y are:

(a) NHR₁R₂, N⁺R₁R₂R₃;

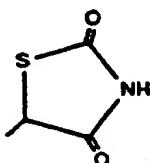
(b)



15 (c) CO₂H;

(d) CH(R₆)CO₂H,

(e) a moiety of the formula:



20 wherein

R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl or t-butoxycarbonyl;

R₄ and R₅ are independently t-butoxycarbonyl or hydrogen; ;

R₆ is hydrogen or hydroxy;

25 and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

Most preferred are those compounds of formula 1 wherein:

the moiety Q is a fused phenyl;

Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy,

30 amino, nitro, sulfonylamino or trifluoromethyl;

Z₂ is hydrogen or, where Z₁ is a halogen, Z₂ is also a halogen;

X is oxygen;

A is C₁-C₅ alkyl, CH₂phenyl, CH₂thienyl, CH₂pyridyl, CH₂furyl, or ethyl piperidine; wherein said phenyl, thienyl, pyridyl, furyl or

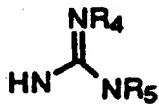
piperidine moiety is optionally substituted with (C₁-C₆)alkyl, benzyl, oxybenzyl phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl or carbomethoxy;

n is an integer from 0-3;

5 Y is a moiety selected from:

(a) NHR₁R₂, N⁺R₁R₂R₃;

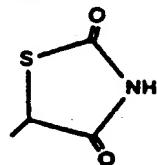
(b)



(c) CO₂H;

10 (d) CH(R₆)CO₂H,

(e) a moiety of the formula:



wherein

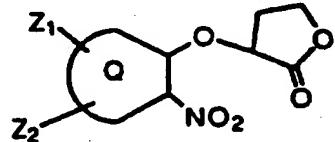
15 R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl or t-butoxycarbonyl;

R₄ and R₅ are independently t-butoxycarbonyl or hydrogen;

R₆ is hydrogen or hydroxy;

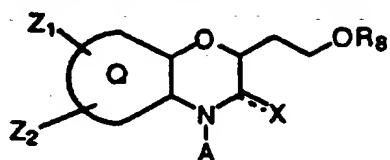
and the pharmaceutically acceptable salts, esters and pro-drug forms
20 thereof.

In another aspect of the present invention, certain novel intermediates useful in the preparation of the final compounds are contemplated. Thus the invention encompasses intermediates of the following formula:



25 wherein the Q moiety is phenyl or pyridyl and Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl; and
Z₂ is hydrogen or a halogen.

Also included are intermediates of the general formula:



wherein the Q moiety is phenyl or pyridyl and Z1 is hydrogen, halogen, C1-C6 alkyl, C1-C6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

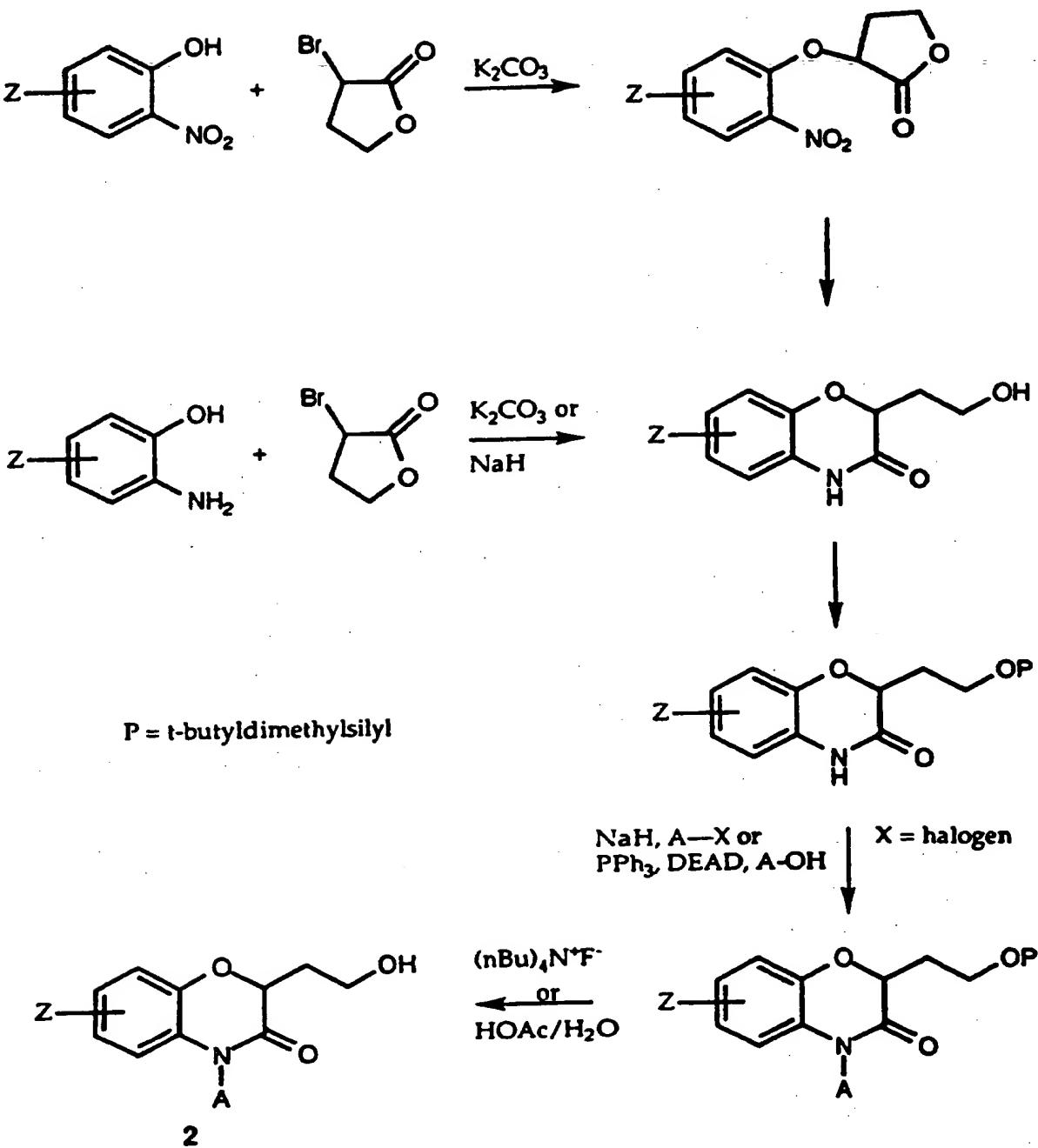
5 Z2 is hydrogen or a halogen, A is C1-C6 alkylaryl or C1-C6 alkylheterocyclyl,
 wherein aryl is biphenyl, naphthyl or phenyl; and heterocyclyl is a 5 or
10 6 membered saturated or unsaturated heterocyclic group containing
 1-4 nitrogen atoms, an oxygen or a sulfur atom; wherein said aryl or
 heterocyclyl group is optionally substituted with (C1-C6)alkyl, benzyl,
 oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro,
 amino, carboxyl, carbo(C1-C4)alkoxy or methylsulfonylamino;
 and R8 is hydrogen or a hydroxy protecting group. A suitable hydroxy
15 protecting group includes any conventional protecting groups for
 hydroxy moieties as routinely used by those skilled in the art such as
 those found in T. Greene, "Protecting Groups in Organic Synthesis", J.
 Wiley and Sons, 1981. These include silyl esters, aliphatic esters and
 aromatic esters such as trimethylsilyl, t-butyldimethylsilyl, acetyl,
20 benzoyl and the like.

The compounds of the present invention are prepared in accordance with the methods described below and illustrated in the following Schemes. The first step in the synthesis involves a novel addition, cyclization reaction of the α -bromo- γ -butyrolactone shown in Scheme 1 with a suitably substituted 2-nitro or 2-aminophenol. The reaction may be carried out in two discrete steps, beginning with known, generally commercially available nitrophenols having most of the definitions for Z cited in the invention description. The solvent is usually DMF and a basic reagent such as K_2CO_3 is needed to drive the reaction to completion. The cyclization step occurs upon reduction of the nitro group with any of the reagent systems known to be useful for this reduction, including palladium catalyzed hydrogenation, nickel and sodium borohydride, and iron-acetic acid. Alternatively, especially in cases where Z is a nitro group or Q is a fused pyridyl, both the

addition and cyclization steps may be carried out in a single procedure using a base, such as K_2CO_3 or NaH , in DMF with or without heating.

Having generated the benzoxazine heterocyclic ring system in this manner, the intermediate alcohol **2** may be prepared by a three step sequence of reactions. Protection of the alcohol group, with a known protecting group such as a t-butyldimethylsilyl derivative or equivalents thereof, is followed by reaction at the 4-position involving nucleophilic displacement of an alkyl or aryl halide under basic conditions: for example, NaH in DMF is highly effective. Alternatively, derivatization of the 4-position nitrogen may be carried out by Mitsunobu reaction of a suitably substituted alcohol. Deprotection of the alcohol with any of the usual fluoride anion reagents or under acidic conditions provides compound **2**.

As is apparent, Scheme 1 depicts the preparation of benzoxazine compounds wherein the "Q" moiety is a fused phenyl. The pyrido-oxazine compounds where the "Q" moiety is a fused pyridyl may be prepared in accordance with the same procedure by substituting a suitably substituted 2-nitro- or 2-amino pyridoxyl moiety for the phenol starting material depicted in Scheme 1. In the remaining synthesis depicted in Schemes 2-10 hereinafter, the pyrido-oxazine compounds may likewise be conveniently substituted for the benzoxazine compounds illustrated in the Schemes.

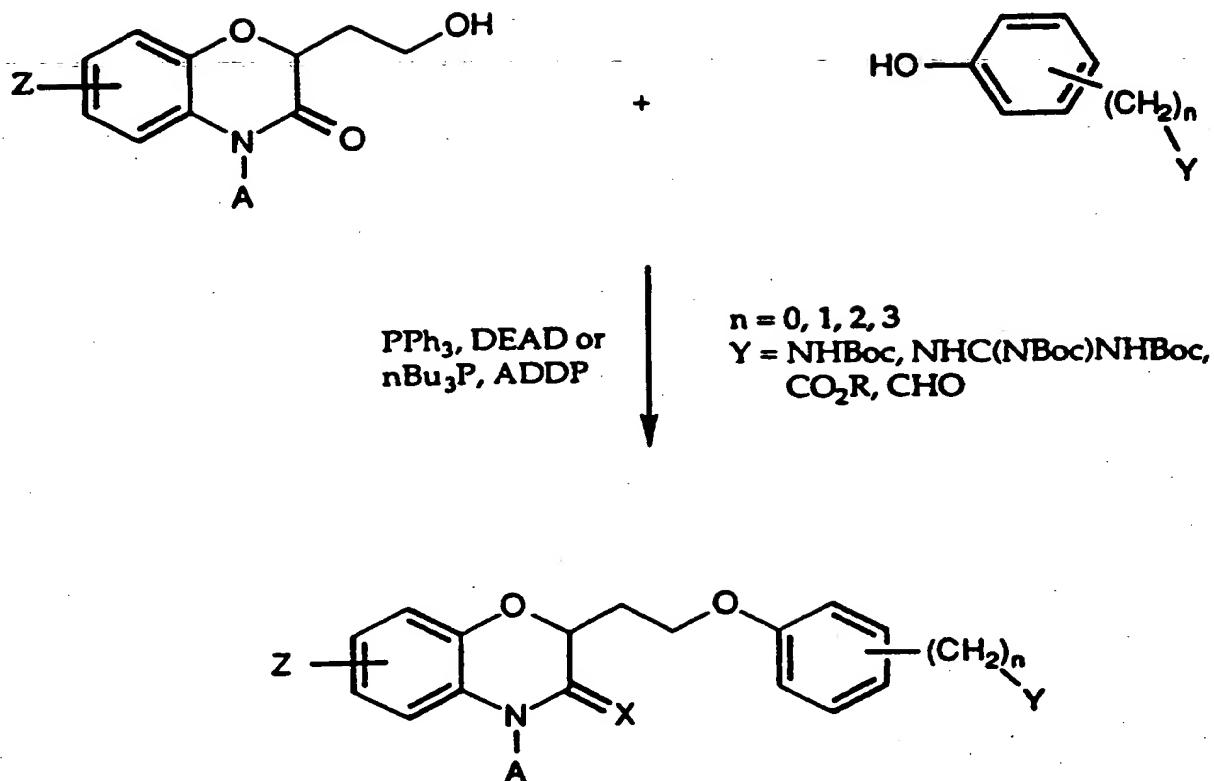


Scheme 1

5 The key step of the synthesis is a coupling reaction of the alcohol **2** with a substituted phenol, by Mitsunobu reaction, as shown in Scheme 2. The Mitsunobu reaction may be one of several variants known in the art; the selection of the appropriate phosphine, azodicarbonyl reagent, and solvent will be at the discretion of the practitioner, based on published precedents
 10 and on empirical results with the particular combination of substrates to be

coupl d. Guidance can be found in the review article by D. L. Hughes, in *Organic Reactions*, 42, 335-656 (1992), and in the detailed examples below. In most cases triphenylphosphine (Ph_3P) and diethylazodicarboxylate (DEAD), or alternatively tributylphosphine (Bu_3P) and (azodicarbonyl)dipiperidine (ADDP), will suffice.

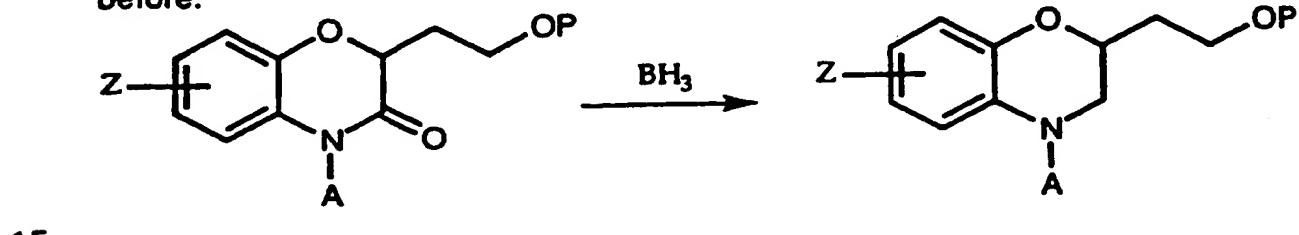
At the time of the Mitsunobu reaction, the group Y will in most cases have to be in a protected form of a more potent compound, or else (for instance when the desired compound is a heterocycle) Y will be a precursor functional group convertible into the desired heterocycle. Once the linkage of the two portions has been established, the group Y is converted, if necessary, into the preferred functional group, as shown in the Schemes below. Suitable protecting groups for guanidines and amines include, but are not limited to, trifluoroacetyl, *t*-butoxycarbonyl (Boc), and benzyloxycarbonyl. Suitable protecting groups for carboxylic acids include, but are not limited to, lower alkyl esters or benzyl esters; suitable precursor groups include olefin, nitrile, or oxazolidine. The chemical processes presented in the Scheme are in general applicable to all definitions of Y.



Scheme 2

5

To obtain those compounds where $X = \text{hydrogen}$, the Mitsunobu coupling reaction is carried out on a reduced derivative of compound 2. The reduction is most easily carried out on the protected precursor of 2 as illustrated in Scheme 3 by using a commercially available borane reagent such as borane-THF complex. After reduction, deprotection as shown in Scheme 1 affords the alcohol which undergoes the Mitsunobu reaction as before.



15

Scheme 3

In Scheme 4, reaction of 2-(4-hydroxyphenyl)ethylamine with di-*t*-butyldicarbonate, to afford a protected phenolic coupling component for the Mitsunobu reaction, is illustrated. A variety of (hydroxyphenyl)alkylamines are commercially available or are known compounds; they can be

5 synthesized by common methods such as reductive amination of benzaldehydes, hydrogenation of arylacetonitriles or aryloxyacetonitriles, reduction of cinnamides or cinnamylamines, etc. Methods for their preparation can be chosen from, but are not limited to, the examples presented herein.

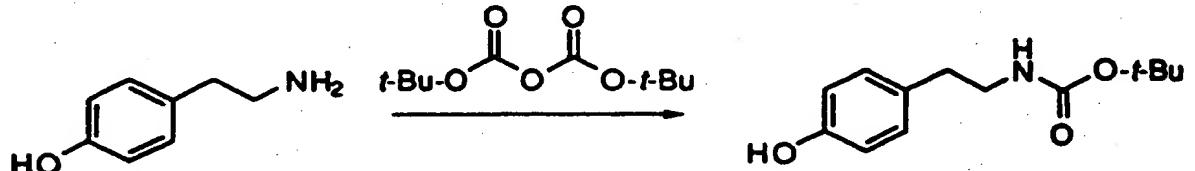
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Also in Scheme 4, the generation of a protected guanidine from the corresponding amine is illustrated, again providing a phenolic component for the Mitsunobu coupling. The illustrated use of N,N'-bis(*t*-butoxycarbonyl)-S-methylisothiourea for this purpose is a known procedure (R. J. Bergeron, J. S. McManis, *J. Org. Chem.*, 52, 1700-1703 (1987); it is in some cases improved by the addition of silver acetate to the reaction mixture. (See also M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *Tetrahedron Letters*, 34, 3389 (1993)). These methods are in general applicable to all amines with the various definitions of Ar, X, W, and n.

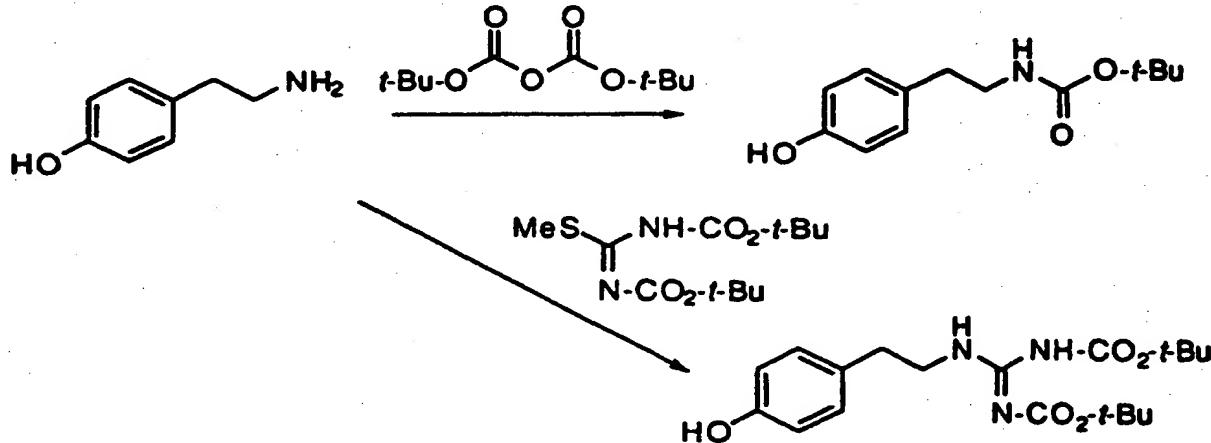
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Alternatively, one can prepare 1 (see description of invention) with Y = NH₂ and then convert the amino group into a guanidino group by the above or by other known methods (e.g., M. S. Bernatowicz, Y. Wu, G. R. Matsueda, *J. Org. Chem.*, 57, 2497-2502 (1992) and references therein).

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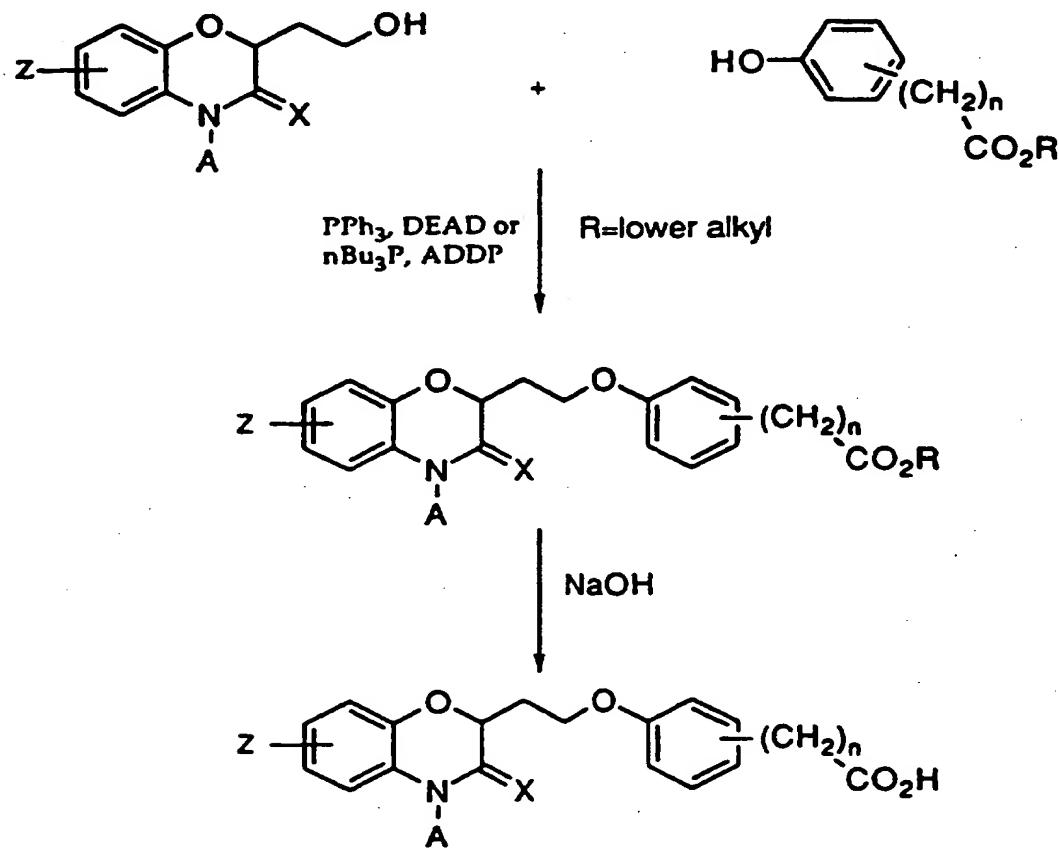


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Scheme 4

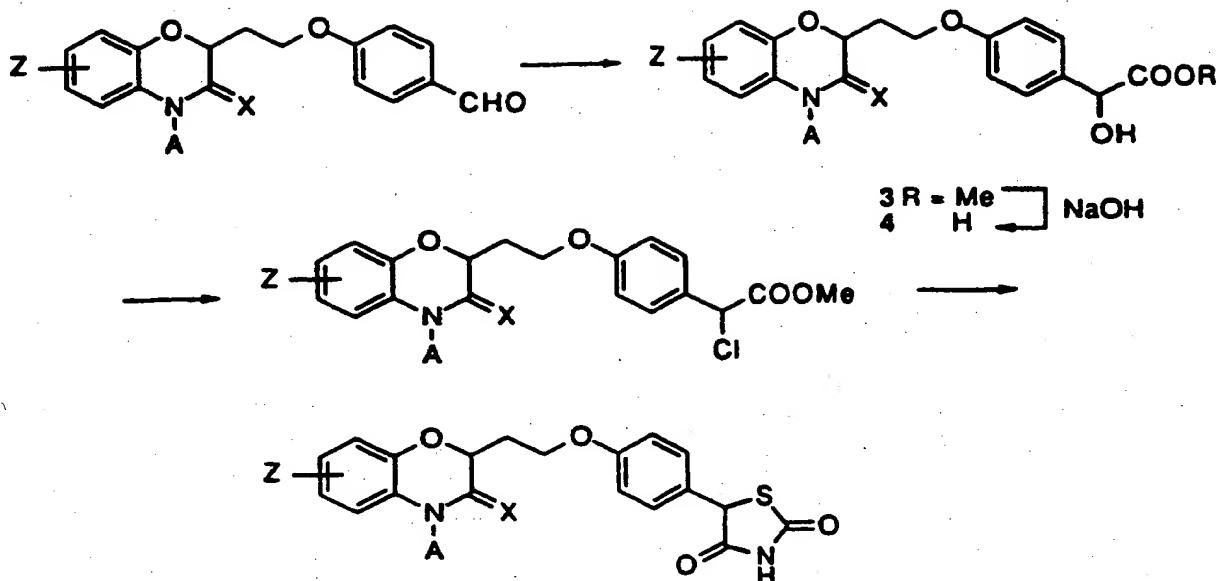
- For compounds where Y is a carboxylic acid (see definition), the starting phenols with the appropriate substitution are known compounds and are commercially available as either the carboxylic acids or the corresponding alkanoic esters. The acids are first protected as the alkanoic esters prior to Mitsunobu coupling in the usual manner as shown in Scheme 5. After coupling, saponification with NaOH provides the final products.



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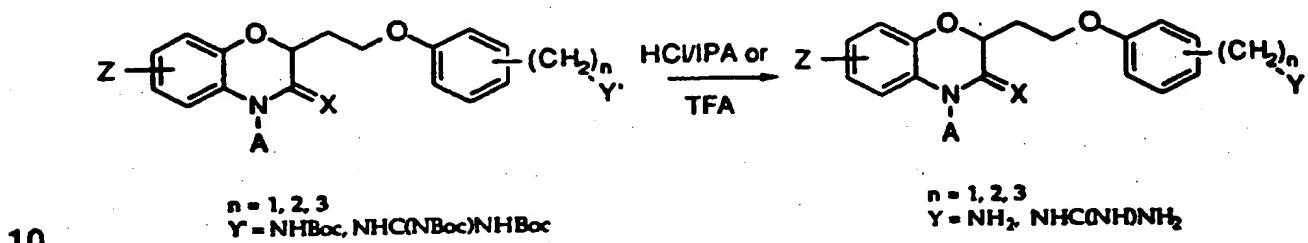
Scheme 5

- Where n is 0 and Y is CHO (Scheme 6), reaction with bromoform and KOH followed by methylation of the crude product provides hydroxy ester 3. Hydrolysis of the ester thus formed, affords the corresponding hydroxy acid 4. The acid 4, may be treated with reagents such as thionyl chloride to generate the chloro derivative, followed by reaction with thiourea to produce the thiazolidinedione also shown in Scheme 6.



Scheme 6

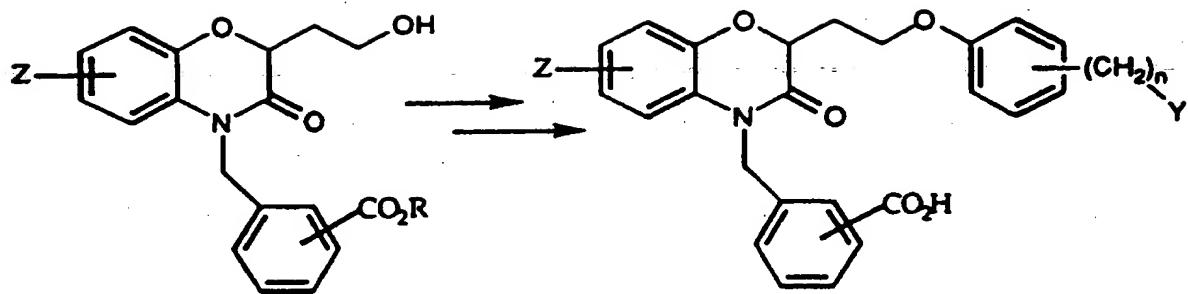
5 For compounds where Y is, in effect, a protected amine or guanidine (Scheme 7), reaction under acidic conditions, for example, trifluoroacetic acid or hydrochloric acid in isopropanol, affords the amine and guanidine salts, respectively.



Scheme 7

15 In the cases where A (see description of invention), is a carboxylic acid substituted benzyl group, the alcohol shown in Scheme 8 may be prepared by the method outlined in Scheme 1, using known benzylic halides bearing a carboxylic ester substituent. The previously described transformations are carried out with the ester in place, followed by hydrolysis of the ester to generate the acid, usually in the final step of the sequence.

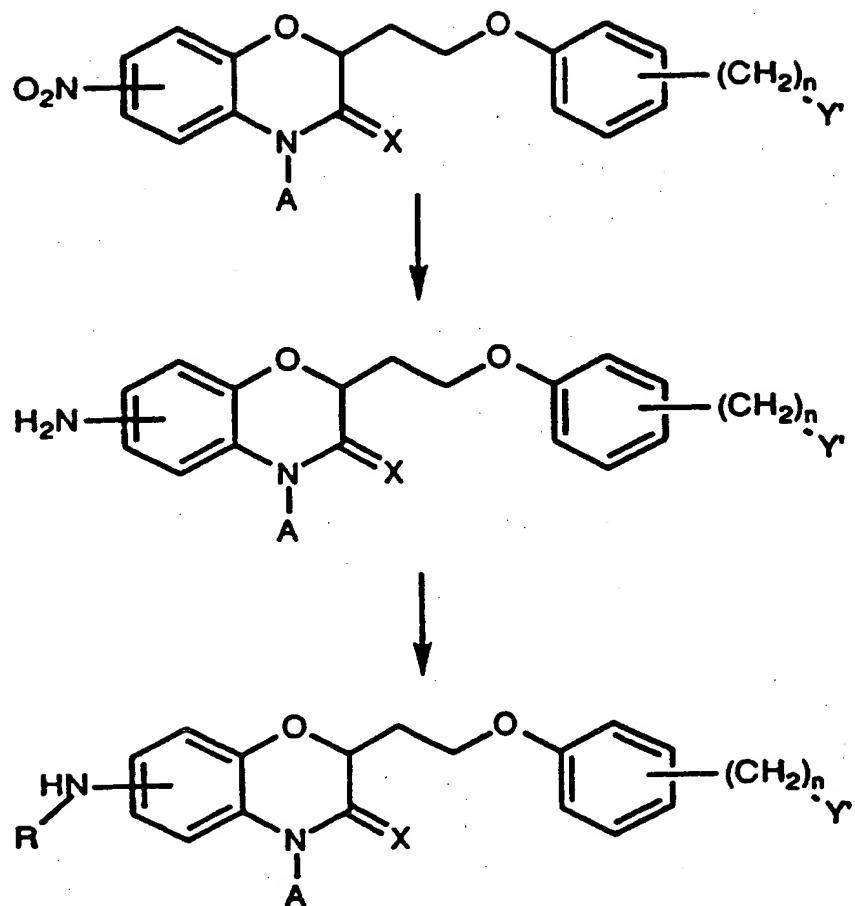
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Scheme 8

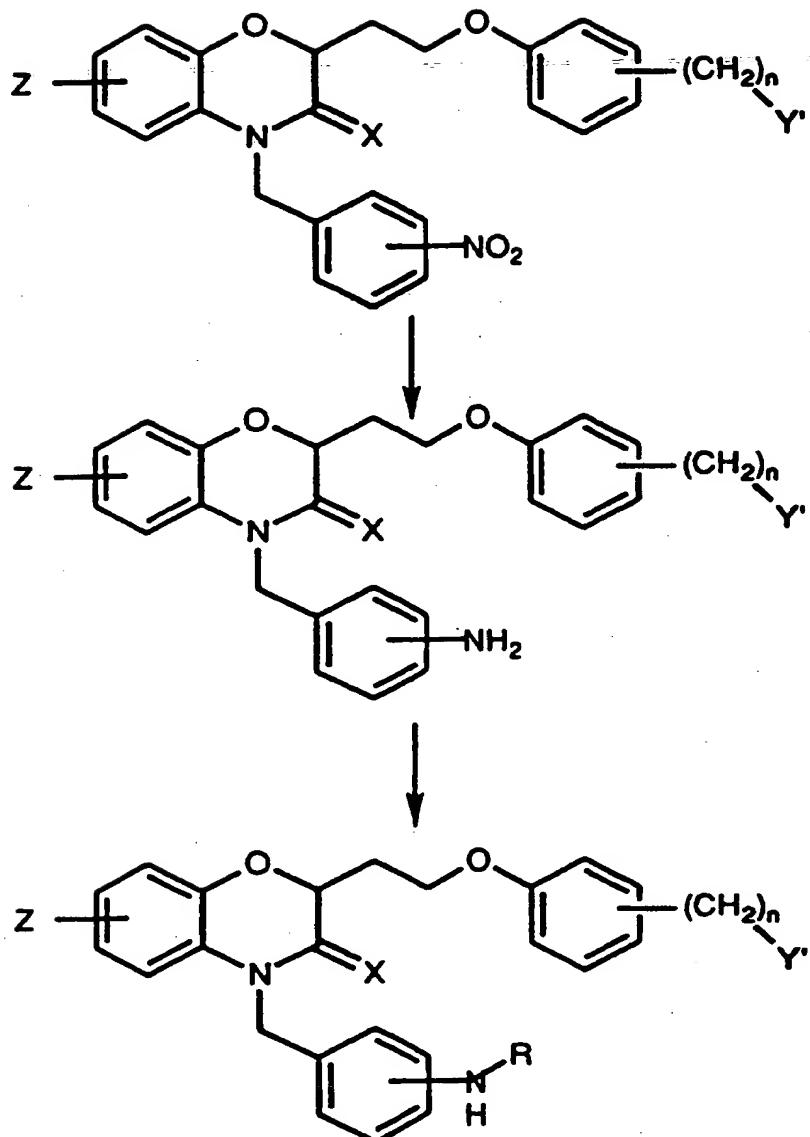
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The transformations outlined in Scheme 1, for preparation of alcohol 2 and the coupling reaction described in Scheme 2 may be carried out on nitro substituted starting materials to afford the products shown in Scheme 9. Reduction of the nitro group with reagents such as iron/acetic acid or palladium catalyzed hydrogenation, can be carried out on, for example, compounds originating from the protected amino or guanidino phenols shown in Scheme 2. Alternatively, the reduction may be effected on the unprotected compounds, provided that no further manipulations are needed. With the protected species, the resulting amine may be further functionalized with electrophilic reagents to afford the products shown in Scheme 9. Similar transformations can be carried out on compounds derived from 2 bearing a nitrobenzyl substituent, as shown in Scheme 10.



R = SO₂R', COR' n = 1, 2, 3
R' = alkyl, aryl Y' = NHBoc, NHC(NBoc)NHBoc

Scheme 9



$R = \text{SO}_2\text{R}', \text{COR}' \quad n = 1, 2, 3$
 $\text{R}' = \text{alkyl, aryl} \quad Y' = \text{NHBOC, NHC(NBoc)NHBOC}$

Scheme 10

- 5 The foregoing reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This will frequently necessitate judgment as to the order of synthetic steps, protection of reactive groups,
- 10

and selection of reaction conditions. Reaction conditions compatible with the substituents employed will be apparent to one skilled in the art, as will be the selection of protecting groups where needed.

5 From formula 1 it is evident that some of the compounds of the invention may have one or more asymmetrical carbon atoms in their structure. It is intended that the present invention include within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of art known principles. Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may 15 also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereospecific reactions.

Suitable pharmaceutical salts are those of inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, 20 nitric acid, phosphoric acid, acetic acid, succinic acid, oxalic acid, malic acid and the like. Suitable salts are also those of inorganic or organic bases, such as KOH, NaOH, Ca(OH)2, Al(OH)3, piperidine, morpholine, ethylamine, triethylamine and the like.

25 Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

The ability of bacteria to quickly respond to changes in the 30 environment is of utmost importance for their survival. Bacteria are capable of rapidly responding and adapting to such diverse stimuli as changes in nutrients, osmolarity, temperature, light, or host environment. These responses may be transient, such as those required for changes in motility or for entry into a host cell. Alternatively, the responses may require major 35 shifts in gene expression and cell morphology, such as those required for sporulation, or for survival within a macrophage. The mechanism by which bacteria are able to sense cues from the physical environment (or from

within the cytoplasm) and process these signals into appropriate responses often involves the so-called "two-component" systems.

As stated above, the treatment method of the present invention is based on the inhibition of this "two-component switch" system. All bacteria use this mechanism to control various adaptive/virulence factors to facilitate establishment of a bacterial population in the environment (for example, a bacterial infection in a host). The system invariably consists of a sensor which either activates a kinase or is a part of the kinase, and which upon stimulation, autophosphorylates. This phosphorylated species is a highly active phosphodonor which immediately transfers its phosphate to a "regulatory" component, which in turn initiates the biological response such as transcription or further phosphotransfer in a cascade which eventually ends in regulation of bacterial gene expression. Although each of the kinases and response regulators has a unique sequence (in fact, even functionally identical proteins have slightly different sequences in different species) they share a homologous biochemical mechanism and they share significant homology in the active site.

As stated, the present invention provides compounds which exhibit antibiotic activity by inhibiting the autophosphorylation of bacterial histidine kinases. They also inhibit the transfer of phosphate from phosphorylated histidine kinases to the aspartyl residues of the phosphate acceptor proteins involved in regulation of bacterial gene expression.

This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and lixirs containing, for example, from about 20% to 50% ethanol, and the like, or

parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

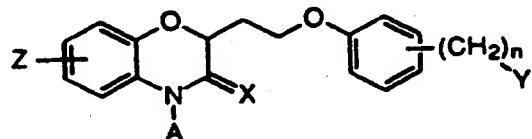
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the

- xt mporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the xtent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of
- 5 microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.
- 10 The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to
- 15 about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture
- 20 with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.
- 25
- The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredients(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the
- 30 composition into the medicament (e.g. tablets).
- 35 The compounds of the present invention have antibacterial activity as determined by the following tests. First, the compounds were tested for their activity in inhibiting the autophosphorylation of Kinase A and the transphosphorylation of SpoOF, two proteins involved in one of the above described signal transduction systems controlling gene expression in bacteria. Representative compounds were then tested for antibacterial

activity against selected organisms by the standard MIC method. The results are set forth below.

- Table 1 lists examples of compounds of the invention, along with their IC₅₀ values in the HPK *in vitro* assay described below, and MIC value ranges for the selected microorganisms identified below. These examples are merely illustrative of the invention, and are not intended to limit the scope of the claims in any way. In Table 1, benzoxazine compounds are listed in accordance with the following formula:

10



15

KEY: Bz = benzyl T = NH₂ G = NHC(NH)NH₂ napMe = naphthylmethyl
pyrMe = pyridylmethyl Cl-Thi = 2-Chloro-4-thienylmethyl Thi = thienylmethyl
BoB = benzyloxybenzyl PBz = phenylbenzyl Thia = 2,4-dioxodihydrothiazole

	Cpd#	A	Z	X	pos.(n)-Y	IC ₅₀	MIC(G+G ⁻)
20	1	3-Cl-Bz	H	O	4(1)-T-Boc	253	8-32/32->128
	2	3-Cl-Bz	H	O	4(1)-T	55	
	3	4-Cl-Bz	H	O	4(1)-T-Boc	283	
	4	4-Cl-Bz	H	O	4(1)-T	47	
	6	4-Cl-Bz	H	O	4(2)-T	61	
	7	4-Cl-Bz	H	O	3(2)-T-Boc	308	
25	8	4-Cl-Bz	H	O	3(2)-T	89	8-16/8->128
	10	4-Cl-Bz	H	O	3(1)-T	122	
	12	2-Cl-Bz	H	O	3(1)-T	140	
	13	2-Cl-Bz	H	O	4(1)-T-Boc	272	
	14	2-Cl-Bz	H	O	4(1)-T	172	
	15	2-Cl-Bz	H	O	3(2)-T-Boc	165	
30	16	2-Cl-Bz	H	O	3(2)-T	74	8-16/8->128
	17	2-Cl-Bz	H	O	4(2)-T-Boc	352	
	18	2-Cl-Bz	H	O	4(2)-T	264	
	19	2-Cl-Bz	H	C	4(1)-G	16	
	20	2-Cl-Bz	H	O	4(2)-G	16	

21	4-Cl-Bz	H	O	4(1)-G	26		
22	4-Cl-Bz	H	H,H	4(2)-G	41	2-4/8->64	
23	3-Cl-Bz	H	H,H	4(2)-G	17	1-2/4->128	
24	3-Cl-Bz	6-Me	O	4(2)-G	56		
5	25	2-Cl-Bz	H	H,H	4(1)-G	23	1-2/8->64
	26	4-Cl-Bz	H	O	4(2)-G	68	2-4/4->128
	27	Bz	H	O	4(2)-G-diBoc	340	
	28	Bz	H	O	4(2)-G	44	
	29	2-OMe-Bz	H	O	4(2)-G	54	
10	31	3-F-Bz	H	O	4(2)-G	46	
	33	3-OMe-Bz	H	O	4(2)-G	145	
	35	3-BoB	H	O	4(2)-G	24	
	36	3-OH-Bz	H	O	4(2)-G	72	
	37	4-OMe-Bz	H	O	4(2)-G	51	
15	38	4-PBz	H	O	4(2)-G	34	
	39	3,5-diCl-Bz	H	O	4(1)-T	46	4-16/4->128
	40	3,5-diCl-Bz	H	O	4(2)-G	24	2/8->128
	42	4-pyrMe	H	O	4(2)-G	444	
	43	1-napMe	H	O	4(2)-G	13	
20	45	2-napMe	H	O	4(2)-G	17	
	46	Thi	H	O	4(2)-G	68	
	47	4-Cl-Thi	H	O	4(2)-G-diBoc	398	
	48	4-Cl-Thi	H	O	4(2)-G	26	
	50	3-Cl-Bz	6-Cl	O	4(2)-G	9	2/4->128
25	52	3-Cl-Bz	6-Ph	O	4(2)-G	36	
	53	3-Cl-Bz	7-CF ₃	O	4(2)-G-diBoc	84	
	54	3-Cl-Bz	7-CF ₃	O	4(2)-G	14	
	55	3-Cl-Bz	7-F	O	4(2)-G	28	
	57	3-Cl-Bz	6,8-diCl	O	4(2)-G	17	
30	58	3-Cl-Bz	7-Me	O	4(2)-G	17	2/4->128
	59	Me	H	O	4(2)-G-diBoc	473	
	60	Me	H	O	4(2)-G	55	16-34/16->64
	61	n-pentyl	H	O	4(2)-G	41	4-8/4-64
	64	3,5-diCl-Bz	H	O	3(2)-T	32	4-8/4->128
35	66	4-Me-Bz	H	H,H	4(2)-G	19	
	68	2,4-diCl-Bz	H	H,H	4(2)-G	17	
	69	3-Cl-Bz	H	O	3(2)-T-Boc	358	
	70	3-Cl-Bz	H	O	3(2)-T	65	8-16/8->128

71	3-Cl-Bz	H	O	4(2)-G-diBoc	300		
72	3-Cl-Bz	H	O	4(2)-G	30	2-4/4->128	
73	3-Cl-Bz	H	O	3(1)-T-Boc	354		
74	3-Cl-Bz	H	O	3(1)-T	81	8-16/≤16->128	
5	76	3-Cl-Bz	H	O	4(3)-T	32	8/8->128
	77	3-Cl-Bz	H	O	4(1)-G-diBoc	51	
	78	3-Cl-Bz	H	O	4(1)-G	32	1-4/4->128
	79	3-Cl-Bz	H	O	4(2)-T	78	8-16/8->128
	80	3-Cl-Bz	7-NO ₂	O	4(2)-G-diBoc	162	
10	82	3-Cl-Bz	7-NO ₂	O	4(2)-T	27	
	84	3-Cl-Bz	7-NO ₂	O	4(2)-G	30	
	87	2-Cl-Bz	7-NO ₂	O	4(1)-G	11	
	89	2-Cl-Bz	6-NO ₂	O	4(2)-G	17	1-4/2->128
	91	3-NO ₂ -Bz	7-NO ₂	O	4(2)-G	33	
15	92	3-Cl-Bz	6-A	O	4(2)-G	34	2-16/4->128
	95	3-NO ₂ -Bz	H	O	4(2)-G	32	
	97	4-NO ₂ -Bz	7-NO ₂	O	4(2)-G	53	
	99	3-NO ₂ -Bz	7-OMe	O	4(2)-G-diBoc	343	
	100	3-NO ₂ -Bz	7-OMe	O	4(2)-G	32	
20	104	4-CO ₂ Me-B	H	O	4(2)-T	24	
	106	3-CO ₂ Me-B	H	O	4(2)-T	166	
	110	4-CO ₂ H-Bz	H	O	4(2)-T	324	
	111	3-CO ₂ H-Bz	H	O	4(2)-T-Boc	113	
	112	3-CO ₂ H-Bz	H	O	4(2)-T	254	
25	127	3-Cl-Bz	H	O	3(2)-CO ₂ H	251	
	134	3-Cl-Bz	H	O	4(0)-Thia	23	
	139	4-NO ₂ -Bz	H	O	4(2)-G	24	
	140	4-OMe-Bz	H	O	4(2)-G-diBoc	343	
	141	2,4-diCl-Bz	H	O	4(2)-G	37	
30	142	4-Cl-Bz	H	O	3(3)-T	42	
	143	2-NO ₂ -Bz	7- NO ₂	O	4(2)-G-diBoc	73	
	144	3-Cl-Bz	H	O	4(2)-T-Boc	348	

In Table 2, activities for pyrido-oxazine compounds of the following formula
 35 where Q is a fused pyridyl moiety are listed:

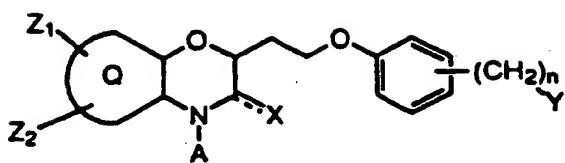


TABLE 2

KEY: Bz = benzyl T = NH₂ G = NHC(NH)NH₂ napMe = naphthylmethyl
 5 pyrMe = pyridylmethyl Cl-Thi = 2-Chloro-4-thienylmethyl Thi = thienylmethyl
 BoB = benzyloxybenzyl PBz = phenylbenzyl Thia = 2,4
 dioxodihydrothiazole

	Cpd#	A	Z ₁ Z ₂	X	pos.(n)-Y	IC ₅₀	MIC(G+G ⁻)
10	25	3-Cl-Bz	H,H	O	4(2)-G	41	
	62	3-Cl-Bz	H,H	O	4(2)-G	174	

The protocols for the above referenced assays are as follows.

15 1. Autophosphorylation of Kinase A and Transphosphorylation of SpoOF Assay

To study the effect of the compounds of the present invention on the signal transduction process in bacteria, the inhibiting effect of the 20 compounds on the sporulation operon proteins Kinase A and SpoOF was examined. Specifically, the inhibition of autophosphorylation of Kinase A and the transphosphorylation of SpoOF was determined in the following assays. The SpoOF response regulator is the primary substrate for phosphorylation by the protein kinase, Kin A, involved in the sporulation process in bacteria. See D. Burbulis, K.A. Trach, J.A. Hoch, *Cell*, **64**, 545-552 (1991). SpoOF and KinA were prepared from recombinant *E. coli* overexpressing the proteins (J. Cavanagh *et al.*, *Amino Acids*, **6**, 131-140 (1994) and references therein).

30 The following stock reagents were either prepared and used promptly or stored at the indicated temperature:

8 X Salts : 2 M KCl (5 mL), 1 M MgCl₂ (800 mL), 1 M CaCl₂ (100 mL),
 10 mg/mL phenylmethylsulfonyl fluoride (200 mL), 1 M dithioreitol (50
 35 mL), 0.25 M Na₂EDTA (32 mL) and H₂O 3.82 mL (-20 °C)

5X Loading Dye: 0.5M TRIS-HCl-pH 6.8 (7.5 mL), 10% SDS (2 mL)
0.1% bromophenol blu (0.5 mL), 100% glycerol (3 mL) and 12.5 M 2-
mercaptoethanol (0.3 mL)

5

1-1.3 mg/mL KinA: 15 mM TRIS-HCl, pH 8.0, 6 mM KCl; 4 mM 2-
mercaptoethanol; 40% glycerol (-20 °C)

10

1 mg/mL SpoOF: 17.5 mM TRIS-HCl, pH 8.0; 0.7 mM KCl ; 0.7 mM
MgCl₂; 0.7 mM CaCl₂; 5mM 2-mercaptoethanol; 30% Glycerol (-20 °C)

15

5% Stacking Gel: 40% 29:1 acrylamide:bis acrylamide (1.25 mL),
0.5 M TRIS-HCl, pH 6.8 (2.5 mL), 10% SDS (0.1mL), D-H₂O (6.15
mL) 10% ammonium persulfate (100 mL) and TEMED (25 mL)

SDS Running Buffer: TRIS-BASE (3.02 g), glycine (14.4 g)
SDS (1 g), D-H₂O (to 1 L)

The reaction mixture was prepared from 8X Salts (87 µL), 1M TRIS,
20 pH 8 (118 µL), 50% glycerol (63 µL), SpoOF (14.1 µL) and KinA (7.0 µL).
Microcentrifuge tubes were charged with the reaction mixture (18.5 µL) and
a 1.0 mM solution of the test compound in 5% DMSO (18.5 µL), and
incubated for 15 min on ice. 100 mM ATP solution (3.0 µl, containing 625
µCi [³²P]ATP) was added, and the mixture left for 10 minutes at room
25 temperature. The reaction was quenched with 5X loading dye (10 µL per
tube) and the samples were loaded on a prepared 5% Stacking Gel, or
stored on dry ice until ready for use. The prepared wells were filled with
SDS Running Buffer, samples were loaded into the wells, and 80 volts were
applied to the gel until the dye front reached the bottom of the stacking gel.
30 The voltage was then increased to 250 volts until electrophoresis was
complete. Radioactive bands in the gel corresponding to phosphorylated
KinA and SpoOF were imaged and quantitated with a phosphoimager.

If either enzyme was inhibited (as evidenced by the absence of
35 labelled protein in the developed gel), an IC₅₀ was calculated by running
the assay with a range of inhibitor concentrations from 1 to 500 µM. After
electrophoresis of the reaction mixtures, percent inhibition was determined
by measuring the concentration of radioactive phosphorus with a

phosphoimager and calculating the values using a software program (BioRad Molecular Analyst). IC₅₀ values of less than 500μM are considered active.

2. MIC Antimicrobial Assay

The *in vitro* antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A2, Vol.10, No.8 "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically - Second Edition."

In this method two-fold serial dilutions of drug in cation supplemented Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFUs/well.

Following inoculation of the microdilution trays, the trays are incubated at 35°C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Tables 1 and 2, compounds of the present invention were tested against a variety of Gram + and Gram - pathogenic bacteria resulting in a range of activities, from 1->128 µg/mL depending on the organism tested. The following test organisms were utilized in the assay:

gram positive bacteria

- Enterococcus faecalis* ATCC 29212
30 *Enterococcus faecalis* oc 3041
Enterococcus faecium oc 2993
Methicillin resistant *Staphylococcus aureus* oc 2089
Methicillin resistant *Staphylococcus aureus* oc 667
Staphylococcus aureus ATCC 29213
35 *Staphylococcus aureus* ATCC 6538
Staphylococcus epidermidis oc 2603

Gram negative bacteria*Escherichia coli* oc 2605*Escherichia coli* oc 2530 ss*Klebsiella pneumoniae* oc 19435 *Pseudomonas aeruginosa* oc 161*Pseudomonas aeruginosa* ATCC 27853

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are 10 illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

15 Methods of preparing the exemplified compounds of the invention are presented below. These examples are intended to illustrate the methods of synthesis, and are not intended to limit the scope of the claims in any way. Abbreviations used: DEAD, diethyl azodicarboxylate; Ph₃P, triphenylphosphine; 20 Bu₃P, tri-n-butylphosphine; THF, tetrahydrofuran; DMF, N,N-dimethylformamide; ADDP, 1,1'-(azodicarbonyl)dipiperidine.

Reference Example 1

Intermediate 9086-181-1

Dihydro-3-(2-nitrophenoxy)-2-(3H)-furanone

5

Method A: 2-nitrophenol (20.2 g, 1eq) was dissolved in DMF (250 ml) and treated with K_2CO_3 (30 g, 1.3 eq), followed by addition of α -bromo- γ -butyrolactone (14.4 ml, 1.2 eq) at room temperature under nitrogen. After stirring 18 h, an additional amount of K_2CO_3 (5g, 0.25 eq) was added. After a total reaction time of 48 h, the reaction was cooled in an ice bath and acetic acid (13.7 ml, 1.65 eq) was added. The crude reaction mixture was poured into water and extracted with EtOAc. The combined extract was concentrated under vacuum and crystallized from ethanol/water to afford white needles (22.4 g 70% yield), mp 112-113°C; IR (KBr) 2939, 1771, 1607, 1586, 1524, 1481, 1356, 1275, 1221, 1194, 1019, 745 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.84 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.62-7.48 (m, 2H), 7.16 (m, 1H), 5.02 (apparent t, $J = 7.4$ Hz, 1H), 4.62-4.52 (m, 1H), 4.45-4.35 (m, 1H), 2.83-2.55 (m, 3H). Anal. Calc'd for $C_{10}H_9NO_5$: C 53.82, H 4.06, N 6.28. Found: C 53.65, H 3.84, N 6.05.

20

Reference Example 2

Intermediate 10353-186-A

Dihydro-3-(4-methyl-2-nitrophenoxy)-2-(3H)-furanone

25 Prepared from 4-methyl-2-nitrophenol by method A in 33% yield as a white solid, MS (Cl) 238 (MH^+); IR (KBr) 3523, 3072, 3005, 1770, 1623, 1577, 1530, 1496, 1463, 1392, 1357, 1282, 1270, 1225, 1194, 1184, 1095, 1020, 992, 804 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.38 (m, 2H), 4.93 (apparent t, $J = 7.4$ Hz, 1H), 4.59 (m, 1H), 4.39 (apparent q, $J = 7.3$ Hz, 1H), 2.78-2.61 (m, 2H), 2.38 (s, 3H). Anal. Calc'd for $C_{11}H_{11}NO_5$: C 55.70 H 4.67, N 5.90. Found: C 55.62, H 4.66, N 5.82.

Reference Example 3

Intermediate 12168-2-1

35 Dihydro-3-(4-methoxy-2-nitrophenoxy)-2-(3H)-furanone

Prepared from 4-methoxy-2-nitrophenol by method A to afford yellow needles in 52% yield, MS (Cl) 254 (MH^+); IR (KBr) 3519, 3102, 3023, 2984,

1765, 1726, 1581, 1532, 1496, 1463, 1442, 1274, 1265, 1229, 1218, 1178,
 1145, 1092, 1068, 1018, 992, 942, 859, 839, 806, 791, 755 cm⁻¹; ¹H NMR
 (CDCl₃) δ 7.52 (d, J = 9.1 Hz, 1H), 7.39, (d, J = 3.1 Hz, 1H), 7.31 (dd, J = 9.1,
 3.0 Hz, 1H), 4.87 (apparent t, J = 7.5 Hz, 1H), 4.55 (m, 1H), 4.36 (m, 1H),
 5 3.87 (s, 3H), 2.82-2.69 (m, 1H), 2.68-2.53 (m, 1H). Anal. Calc'd for
 C₁₁H₁₁NO₆: C 52.18, H 4.38, N 5.53. Found: C 52.19, H 4.50, N 5.43.

Reference Example 4

Intermediate 11653-187

10 Dihydro-3-(5-methoxy-2-nitrophenoxy)-2-(3H)-furanone

Prepared from 5-methoxy-2-nitrophenol by method A in 53% yield, mp 109-
 110°C; MS (CI) MH⁺254; IR (KBr) 3517, 3100, 3075, 2994, 2955, 2931,
 2852, 1484, 1258, 1079, 714 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.98 (d, 1H, J =
 15 9.1 Hz), 7.02 (d, 1H, J = 2.5 Hz), 6.76 (dd, 1H, J = 2.5, 9.2 Hz), 5.62 (t, 1H, J =
 8.7 Hz), 4.48 (dt, 1H, J = 2.4, 8.8 Hz), 4.28 (m, 1H), 3.88 (s, 3H), 2.89-2.73
 (m, 1H), 2.38-2.29 (m, 1H). Anal. Calc'd for C₁₁H₁₁NO₆: C 52.18, H 4.38, N
 5.53. Found: C 51.97, H 4.18, N 5.45.

20 Reference Example 5

Intermediate 11578-25

Dihydro-3-(3-methyl-2-nitrophenoxy)-2(3H)-furanone

Prepared from 3-methyl-2-nitrophenol by method A in 41% yield. A portion
 25 of this material was crystallized from CH₂Cl₂/ether to afford a white solid, mp
 82-84°C; IR (KBr) 2946, 1792, 1530, 1294, 1275, 1182, 1118, 1014, 994,
 777, 638 cm⁻¹; ¹H NMR (CDCl₃) δ 2.32 (s, 3H), 2.45-2.57 (m, 1H), 2.63-2.74
 (m, 1H), 4.32-4.40 (m, 1H), 4.48-4.55 (m, 1H), 4.96 (t, J = 7.4 Hz, 1H), 6.97
 (dd, J = 7.1, 0.6 Hz, 1H), 7.24-7.36 (m, 2H); MH⁺ at m/z = 238; Anal. Calc'd
 30 for C₁₁H₁₁NO₅: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.61; H, 4.62; N, 5.87.

Reference Example 6

Intermediate 11578-61

Dihydro-3-(4-chloro-2-nitrophenoxy)-2(3H)-furanone

35

Prepared from 4-chloro-2-nitrophenol by Method A in 60% yield and isolated
 as a yellow solid, mp 136-140°C; IR (KBr) 3110, 1786, 1771, 1608, 1527,
 1488, 1359, 1276, 1193, 1180, 1020, 825, 734 cm⁻¹; ¹H NMR (CDCl₃) δ

2.57-2.83 (m, 2H), 4.35-4.45 (m, 1H), 4.54-4.63 (m, 1H), 4.98 (t, $J = 7.4$ Hz, 1H), 7.48-7.56 (m, 2H), 7.85 (d, $J = 2.3$ Hz, 1H); MH^+ at m/z = 258; Anal. Calc'd for $C_{10}H_8ClNO_5$: C, 46.62; H, 3.13; N, 5.44. Found: C, 46.61; H, 3.11; N, 5.20.

5

Reference Example 7

Intermediate 11578-62

Dihydro-3-(4-carbomethoxy-2-nitrophenoxy)-2(3H)-furanone

10

Prepared from 4-carbomethoxy-2-nitrophenol by Method A in 30% yield using equal portions of reagents. This material was isolated directly from the aqueous workup as a beige solid, mp 99-101°C; IR (KBr) 2958, 1780, 1726, 1618, 1531, 1348, 1300, 1270, 1179, 1127, 756 cm^{-1} ; ^1H NMR (CDCl_3) δ

15 2.62-2.85 (m, 2H), 3.95 (s, 3H), 4.44 (dt, $J = 9.3, 7.2$ Hz, 1H), 4.58-4.65 (m, 1H), 5.14 (t, $J = 7.3$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 8.24 (dd, $J = 8.8, 2.1$ Hz, 1H), 8.52 (d, $J = 2.1$ Hz, 1H); MH^+ at m/z = 282; Anal. Calc'd for $C_{12}H_{11}NO_7 \cdot 0.3H_2O$: C, 50.29; H, 4.08; N, 4.89. Found: C, 50.03; H, 3.85; N, 4.68.

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Reference Example 8

Intermediate 11578-32

Dihydro-3-(4-phenyl-2-nitrophenoxy)-2(3H)-furanone

25 Prepared from 4-benzyl-2-nitrophenol by Method A in 54% yield as a yellow crystalline solid, mp 117-119°C; IR (KBr) 2931, 1785, 1625, 1535, 1346, 1334, 1279, 1261, 1156, 1022, 756 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.64-2.85 (m, 2H), 4.42 (q, $J = 7.3$ Hz, 1H), 4.57-4.65 (m, 1H), 5.05 (t, $J = 7.3$ Hz, 1H), 7.40-7.59 (m, 6H), 7.78 (dd, $J = 8.7, 2.4$ Hz, 1H), 8.07 (d, $J = 2.4$ Hz, 1H); Anal. Calc'd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.00; H, 4.20; N, 4.59.

Reference Example 9

Intermediate 11578-50

35 Dihydro-3-(4-trifluoromethyl-2-nitrophenoxy)-2(3H)-furanone

Prepared from 4-trifluoromethyl-2-nitrophenol by Method A in 51% yield using equal portions of reagents. This material was isolated as a white

solid, mp 128-129°C; IR (KBr) 3100, 2995, 1782, 1626, 1537, 1358, 1329, 1283, 1159, 1131, 1098, 998, 822 cm⁻¹; ¹H NMR (CDCl₃) δ 2.63-2.86 (m, 2H), 4.40-4.48 (m, 1H), 4.58-4.65 (m, 1H), 5.14 (t, J = 7.4 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 8.8, 1.9 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H); MH⁺ at 5 m/z = 292; Anal. Calc'd for C₁₁H₈F₃NO₅: C, 45.22; H, 3.10; N, 4.79. Found: C, 45.37; H, 2.77; N, 4.81.

Reference Example 10

Intermediate 11578-40

10 Dihydro-3-(5-fluoro-2-nitrophenoxy)-2(3H)-furanone

Prepared from 5-fluoro-2-nitrophenol by Method A in 65% yield using equal portions of reagents. This material was isolated as an off-white solid after crystallization from CH₂Cl₂/ether, mp 98-100°C; IR (KBr) 3055, 1773, 1619, 1591, 1508, 1350, 1284, 1024, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 2.62-2.85 (m, 2H), 4.38-4.46 (m, 1H), 4.57-4.65 (m, 1H), 5.01 (t, J = 7.3 Hz, 1H), 7.23-7.27 (m, 1H plus CHCl₃), 7.96 (dd, J = 9.1, 5.8 Hz, 1H); MH⁺ at m/z = 242; Anal. Calc'd for C₁₀H₈FNO₅: C, 49.80; H, 3.34; N, 5.81. Found: C, 49.85; H, 3.24; N, 5.78.

20 Reference Example 11

Intermediate 11578-38

Dihydro-3-(5-methyl-2-nitrophenoxy)-2(3H)-furanone

25 Prepared from 5-methyl-2-nitrophenol by Method A in 22% yield using equal portions of reagents. This material was crystallized from CH₂Cl₂/ether to afford a white solid, mp 68-70°C; IR (KBr) 3003, 2950, 2928, 1774, 1516, 1355, 1189, 1023, 947 cm⁻¹; ¹H NMR (CDCl₃) δ 2.43 (s, 3H), 2.58-2.81 (m, 2H), 4.35-4.43 (m, 1H), 4.55-4.62 (m, 1H), 4.99 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 7.79 (d, J = 8.3 Hz, 1H); MH⁺ at m/z = 238; Anal. Calc'd for C₁₁H₁₁NO₅: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.68; H, 4.62; N, 5.85.

Reference Example 12

Intermediate 11578-22-Precursor

35 Dihydro-3-(4,6-dichloro-2-nitrophenoxy)-2(3H)-furanone

Prepared from 4,6-dichloro-2-nitrophenol by Method A in 20% yield as an orang solid and used without further purification; IR (KBr) 3086, 1779, 1542, 1457, 1353, 1250, 1222, 1152, 1066, 995, 877 cm⁻¹; ¹H NMR (CDCl₃) δ 2.62-2.81 (m, 2H), 4.35-4.42 (m, 1H), 4.59-4.66 (m, 1H), 5.02 (t, J = 6.6 Hz, 5 H), 7.67 (d, J = 2.6 Hz, 1H), 7.86 (d, J = 2.6 Hz); MH⁺ at m/z 292.

Reference Example 13

Intermediate 9086-183-1

10 3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

Method B: Intermediate 9086-181-1, (11.9 g, 1eq, Reference Example 1) was reacted with H₂ at 50 psi in a Parr shaker bottle containing 10% Pd/C (1.8 g, 15% w/w) in EtOH (200 ml) for 13 h. The catalyst was removed by filtration and the filtrate concentrated under vacuum. The crude product was triturated with hot Et₂O to afford the benzoxazinone in 87% yield as a white powder, mp 65-69°C; IR (KBr) 3298, 3076, 2993, 2917, 1677, 1613, 1505, 1439, 1410, 1312, 1275, 1231, 1119, 1104, 1059, 805, 745, 689 cm⁻¹; ¹H NMR (CDCl₃) δ 8.29 (br s, 1H), 7.01-6.95 (m, 3H), 6.82 (m, 1H), 4.76 (dd, J = 7.6, 5.5 Hz, 1H), 3.91 (m, 2H), 2.35-2.13 (m, 3H). Calc'd for C₁₀H₁₁NO₃: C 62.17, H 5.74, N 7.25. Found: C 62.01, H 5.48, N 6.95.

Reference Example 14

Intermediate 11653-189A

25 3,4-Dihydro-2-(2-hydroxyethyl)-7-methoxy-3-oxo-2H-1,4-benzoxazine

Method C: NaBH₄ (2.7 g, 6 eq.) was gradually added to a stirring mixture of intermediate 11653-187 (3.0 g, 11.8 mmol, Reference Example 4) and NiCl₂·6H₂O (11.2g, 4 eq.) in methanol (75 ml) at 0°C. The resulting dark reaction was allowed to return to room temperature slowly. After 2 days, 2N HCl was carefully added to the reaction mixture until gas evolution stopped. The resulting mixture was diluted with water and extracted with EtOAc. The combined EtOAc layers were washed with saturated NaHCO₃ then concentrated in vacuo to afford a 66% yield of a pale yellow solid, mp 123-30 126°C; MS (Cl) MH⁺224; IR (KBr) 3475, 3307, 3188, 3066, 2931, 2892, 2835, 1769, 1664, 1450, 1327, 1258, 1224, 925 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.15 (br s, 1H), 6.80 (d, 1H, J = 8.5Hz), 6.52 (d, 1H, J = 2.6Hz), 6.46 (dd, 1H, J = 2.6, 8.5Hz), 4.67 (dd, 1H, J = 4.6, 8.8Hz), 4.05 (t, 1H, J = 5.4Hz), 3.79 (m,

2H), 3.74 (s, 3H), 2.16 (m, 1H), 2.01 (m, 1H). Anal. Calc'd for C₁₁H₁₃NO₄: C 59.19, H 5.87, N 6.27. Found: 58.87, 5.80, N 6.09.

Reference Example 15

Intermediate 11653-29A

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3,4-Dihydro-2-(2-hydroxyethyl)-7-nitro-3-oxo-2H-1,4-benzoxazine

Method D: 2-amino-5-nitrophenol (13.5 g, 87.6 mmol, 1 eq.) and α -bromo- γ -butyrolactone (8.0 ml, 96.3 mmol, 1.1 eq.) were added to a stirring mixture of DMF (80 ml) and potassium carbonate (12.1 g, 87.6 mmol). After refluxing 5 hours and returning to room temperature, the reaction was poured into an equal volume of ice water and was stirred 15 minutes before being filtered. The resulting brown solid was dried in vacuo at 65°C to afford a 45% yield of the product, mp 177-178°C; MS (FAB) MH⁺ 239; IR (KBr) 3541, 3204, 3095, 3037, 2929, 2888, 1699, 1599, 1508, 1480, 1417, 1389, 1342, 1299, 1136, 1034, 798, 617, 499 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 11.32 (br s, 1H), 7.91 (dd, 1H, J = 2.4, 8.7 Hz), 7.79 (s, 1H), 7.05 (d, 1H, J = 8.7 Hz), 4.82 (dd, 1H, J = 3.8, 9.0 Hz), 4.70 (br s, 1H), 3.59 (m, 2H), 1.98 (m, 1H), 1.90 (m, 1H). Anal. Calc'd for C₁₀H₁₀N₂O₅: C 50.42, H 4.23, N 11.76. Found: C 50.37, H 4.20, N 11.43.

Reference Example 16

Intermediate 12168-6-1

3,4-Dihydro-2-(2-hydroxyethyl)-6-methoxy-3-oxo-2H-1,4-benzoxazine

25

Prepared from intermediate 12168-2-1 (Reference Example 3) as a light grey solid in 76% yield by method B, mp 111-113°C; MS (Cl) 224 (MH⁺); IR (KBr) 3472, 3337, 3196, 3113, 3055, 2996, 2898, 2832, 1684, 1626, 1611, 1520, 1501, 1466, 1403, 1312, 1292, 1264, 1229, 1192, 1162, 1082, 796, 785 cm⁻¹; ¹H NMR (CDCl₃) δ 7.99 (br s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.52 (dd, J = 8.8, 2.8 Hz, 1H), 6.37 (d, J = 2.8 Hz, 1H), 4.70 (dd, J = 7.5, 5.4 Hz, 1H), 3.90 (m, 2H), 3.77 (s, 3H), 2.21 (m, 2H). HRMS Calc'd for C₁₁H₁₃NO₄ (MH⁺): 224.0922. Found: 224.0974.

35

Reference Example 17

Intermediate 10353-189-1

3,4-Dihydro-2-(2-hydroxyethyl)-6-methyl-3-oxo-2H-1,4-benzoxazine

Prepared by method B from intermediate 10353-186-A (Reference Example 2) and isolated in 70% yield as a white solid, MS (Cl) 208 (MH⁺); IR (KBr) 3337, 3196, 3099, 2919, 1681, 1609, 1523, 1498, 1409, 1365, 1232, 1058, 5 806 cm⁻¹; ¹H NMR (CDCl₃) δ 7.96 (br s, 1H), 6.90 (d, J = 9.1 Hz, 1H), 6.80 (d, 9.1 Hz, 1H), 6.61 (s, 1H), 4.72 (apparent t, J = 7.3 Hz, 1H), 3.90 (apparent q, J = 5.4 Hz, 2H), 2.32-2.15 (m, 3H), 2.30 (s, 3H). Anal. Calc'd for C₁₁H₁₃NO₃: C 63.76, H 6.32, N 6.76. Found: C 63.54, H 6.20, N 6.76.

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Reference Example 18

Intermediate 10353-184-B

3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-6-trifluoromethyl-2H-1,4-benzoxazine

15 Prepared from intermediate 11578-50 (Reference Example 9 by method B and isolated in 54% yield as a fluffy white solid, MS (Cl) 262 (MH⁺); IR (KBr) 3468, 3202, 3113, 3044, 2962, 2888, 1696, 1622, 1496, 1402, 1336, 1215, 1159, 1124, 1111, 1058, 878, 827, 807 cm⁻¹; ¹H NMR (CDCl₃) δ 8.01 (br s, 1H), 7.28 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 4.86 (dd, J = 8.2, 5.2 Hz, 1H), 3.92 (apparent dd, J = 12.7, 5.6 Hz, 2H), 2.38-2.17 (m, 1H), 1.92 (t, J = 5.6 Hz, 1H). Calc'd for C₁₁H₁₀F₃NO₃: C 50.58, H 3.86, N 5.36. Found: C 50.52, H 3.86, N 5.28. HRMS Calc'd for C₁₁H₁₀F₃NO₃ (MH⁺): 262.0691. Found: 262.0740.

25

Reference Example 19

Intermediate 11578-28

3,4-Dihydro-2-(2-hydroxyethyl)-5-methyl-3-oxo-2H-1,4-benzoxazine

Prepared from intermediate 11578-25 (Reference Example 5) by Method C
30 using 3 eq of NiCl₂·6H₂O and 6 eq of NaBH₄, and isolated by flash chromatography (ether elution) in 39% yield as a white solid, mp 147-149°C; IR (KBr) 3221, 1683, 1502, 1480, 1266, 1225, 1099, 1057, 770, 723 cm⁻¹; ¹H NMR (CDCl₃) δ 2.14-2.32 (m, 3H), 2.27 (s, 3H), 4.71 (q, J = 5.3 Hz, 2H), 4.71 (dd, J = 5.5, 7.4 Hz, 1H), 6.82-6.94 (m, 3H), 8.01 (br s, 1H); MH⁺ at m/z = 208; Anal. Calc'd for C₁₁H₁₃NO₃: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.38; H, 6.24; N, 6.72.

Reference Example 20

Intermediate 11578-68

6-Chloro-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

- 5 Prepared from intermediate 11578-61 (Reference Example 6) by Method C using 3 eq of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and 6 eq of NaBH_4 . Isolated in 66% yield as a white solid, mp 135-138°C; IR (KBr) 3475, 2956, 1690, 1498, 1385, 1059, 809 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.95-2.08 (m, 1H), 2.12-2.23 (m, 1H), 3.33 (br s, 1H plus DHO), 3.77-3.82 (m, 2H), 4.69 (dd, $J = 8.9, 4.4$ Hz, 1H), 6.87 (s, 2H), 6.92 (s, 1H), 10.5 (br s, 1H); MH^+ at m/z = 228; Anal. Calc'd for $\text{C}_{10}\text{H}_{10}\text{ClNO}_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 53.15; H, 4.50; N, 6.16.
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Reference Example 21

Intermediate 11578-72

6-Carbomethoxy-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

- Prepared from intermediate 11578-62 (Reference Example 7) by Method C using 3 eq of $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and 6 eq of NaBH_4 . and isolated from EtOAc extraction in 51% yield as a white solid, mp 167-169°C; IR (KBr) 3428, 1729, 1688, 1494, 1400, 1305, 1214, 1049, 764 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.93-2.05 (m, 1H), 2.10-2.16 (m, 1H), 3.34 (v br s, 1H), 3.75-3.78 (m, 2H), 3.86 (s, 3H), 4.77 (dd, $J = 9.1, 4.1$ Hz, 1H), 7.00 (d, $J = 8.2$ Hz, 1H), 7.57-7.62 (m, 2H), 10.65 (s, 1H); Anal. Calc'd for $\text{C}_{12}\text{H}_{13}\text{NO}_5 \cdot 0.2\text{H}_2\text{O}$: C, 56.56; H, 5.30; N, 5.50. Found: C, 56.71; H, 5.18; N, 5.35.
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- 25

Reference Example 22

Intermediate 11578-36

3,4-Dihydro-2-(2-hydroxyethyl)-6-phenyl-3-oxo-2H-1,4-benzoxazine

- 30 Prepared by intermediate 11578-32 (Reference Example 8) by Method C in 55% yield and was isolated as a white crystalline solid, mp 170-171°C; IR (KBr) 3428, 1682, 1605, 1489, 1403, 1237, 1030, 863, 762 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 1.81-1.90 (m, 1H), 1.92-2.01 (m, 1H), 3.53-3.63 (m, 2H), 4.69 (dd, $J = 9.2, 3.9$ Hz, 1H), 7.04 (d, $J = 8.3$ Hz, 1H), 7.13 (d, $J = 2.0$ Hz, 1H), 7.21 (dd, $J = 8.4, 2.1$ Hz, 1H), 7.31-7.36 (m, 1H), 7.45 (t, $J = 7.5$ Hz, 2H), 7.54 (d, $J = 7.3$ Hz, 2H), 10.78 (s, 1H); MH^+ at m/z = 270; Anal. Calc'd for $\text{C}_{16}\text{H}_{15}\text{NO}_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.06; H, 5.53; N, 5.16.
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Reference Example 23

Intermediate 11578-42

3,4-Dihydro-7-fluoro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

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Prepared from intermediate 11578-40 (Reference Example 10) by Method C (reaction time of 3 days) in 43% yield to afford a white solid, mp 136-138°C; IR (KBr) 3474, 3199, 3087, 1676, 1514, 1425, 1150, 1113, 1054, 845 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.95-2.07 (m, 1H), 2.12-2.23 (m, 1H), 3.79 (q, J = 5.2 Hz, 2H), 4.01 (t, J = 5.4 Hz, 1H), 4.71 (dd, J = 8.8, 4.5 Hz, 1H), 6.59-6.70 (m, 2H), 6.85 (dd, J = 8.6, 5.5 Hz, 1H), 10.34 (br s, 1H); MH⁺ at m/z = 121; Anal. Calc'd for C₁₀H₁₀FNO₃: C, 56.87; H, 4.77; N, 6.63. Found: C, 56.75; H, 4.74; N, 6.56.

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Reference Example 24

Intermediate 11578-45

3,4-Dihydro-2-(2-hydroxyethyl)-7-methyl-3-oxo-2H-1,4-benzoxazine

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Prepared from intermediate 11578-38 (Reference Example 11) by Method C to afford a white crystalline solid in 49% yield after crystallization from EtOAc, mp 143-144°C; IR (KBr) 3468, 3069, 1664, 1520, 1421, 1260, 1154, 1135, 1057, 931, 802 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.72-1.86 (m, 1H), 1.87-2.00 (m, 1H), 2.21 (s, 3H), 3.54-3.60 (m, 2H), 4.59 (dd, J = 9.4, 3.9 Hz, 1H), 4.65 (t, J = 5.3 Hz, 1H), 6.72-6.78 (m, 3H), 10.58 (s, 1H); MH⁺ at m/z = 208; Anal. Calc'd for C₁₁H₁₃NO₃: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.73; H, 6.30; N, 6.67.

Reference Example 25

Intermediate 11578-22

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6,8-Dichloro-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

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Prepared from dihydro-3-(3,5-dichloro-2-nitrophenoxy)-2-(3H)-furanone by Method C to afford the product as a white solid in 72% yield, mp 174-176°C; IR (KBr) 3056, 1702, 1598, 1478, 1386, 1227, 1055, 853 cm⁻¹; ¹H NMR (DMSO-d₆) δ 1.77-1.87 (m, 1H), 1.89-1.95 (m, 1H), 3.55-3.63 (m, 2H), 4.72 (t, J = 5.2 Hz, 1H), 4.82 (dd, J = 9.6, 3.7 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 11.00 (br s, 1H); MH⁺ at m/z = 262; Anal. Calc'd for C₁₀H₉Cl₂NO₃: C, 45.83; H, 3.46; N, 5.34. Found: C, 45.82; H, 3.49; N, 5.29.

Reference Example 26

Intermediate 11653-20A

3,4-Dihydro-2-(2-hydroxyethyl)-6-nitro-3-oxo-2H-1,4-benzoxazine

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Prepared from 2-amino-4-nitrophenol by method D in 35% yield, mp 173.5-175°C; MS (FAB) MH^+ 239; IR (KBr) 3401, 3092, 2932, 1595, 1536, 1499, 1323, 1213, 1144, 1100, 945, 474 cm^{-1} ; 1H NMR (DMSO- d_6) δ 11.06 (br s, 1H), 7.85 (dd, 1H, J = 2.59, 8.90Hz), 7.74 (d, 1H, J = 2.54Hz), 7.17 (d, 1H, J = 8.90Hz), 4.88 (dd, 1H, J = 3.88, 8.90Hz), 4.71 (m, 1H), 3.56 (m, 2H), 2.03 (m, 1H), 1.90 (m, 1H). Anal. Calc'd for $C_{10}H_{10}N_2O_5$: C 50.42, H 4.23, N 11.76. Found: C 50.48, H 4.21, N 11.44.

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Reference Example 27

Intermediate 11653-156-A

3,4-Dihydro-6-fluoro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

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Prepared from 2-amino-4-fluorophenol by method D in 22% yield, mp 126-129.5°C; MS (Cl) MH^+ 212; IR (KBr) 3349, 3199, 3109, 3054, 2981, 2893, 1621, 1517, 1500, 1364, 1105, 1009, 946 cm^{-1} ; 1H NMR (DMSO- d_6) δ 10.78 (br s, 1H), 6.98 (dd, 1H, J = 5.1, 8.8 Hz), 6.77 (d, 0.5H, J = 3.0 Hz), 6.74 (d, 0.5H, J = 3.0 Hz), 6.70 (m, 0.5H), 6.67 (d, 0.5H, J = 3.0 Hz), 4.65 (m, 2H), 3.59 (m, 2H), 1.96 (m, 1H), 1.79 (m, 1H). Anal. Calc'd for $C_{10}H_{10}FNO_3$: C 56.87, H 4.77, N 6.63. Found: C 56.55, H 4.91, N 6.54.

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Reference Example 28

Intermediate 12168-5-1

3,4-Dihydro-2-(2-t-butylidemethylsilyloxyethyl)-6-methyl-

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3-oxo-2H-1,4-benzoxazine

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Method E: Intermediate 10353-189-1 (1.6 g, 1eq, Reference Example 17), was dissolved in DMF (4 ml) and treated, sequentially, with chloro *t*-butylidemethylsilane (1.4 g, 1.2 eq) and imidazole (1.3 g, 2.5 eq) while stirring in a nitrogen atmosphere. After 18 h, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was concentrated and the product isolated in 93% yield, as a white powder by crystallization from MeOH/water, MS (Cl) 322 (MH^+); IR (KBr) 2953, 2927, 2883, 2856, 1698,

1609, 1523, 1496, 1360, 1234, 1119, 1093, 842, 832, 811, 778 cm⁻¹; ¹H NMR (CDCl₃) δ 8.27 (br s, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.76 (dd, J = 8.1, 1.7 Hz, 1H), 6.61 (d, J = 1.7 Hz, 1H), 4.72, (dd, J = 9.7, 3.7 Hz, 1H), 3.95-3.78 (m, 2H), 2.28 (s, 3H), 2.20 (m, 1H), 2.00 (m, 1H), 0.90 (s, 9H), 0.70 (s, 3H). Anal, 5 Calc'd for C₁₇H₂₇NO₃Si: C 63.51, H 8.47, N 4.36. Found: C 63.90, H 8.44, N 4.28.

Reference Example 29

Intermediate 12168-8-1

10 3,4-Dihydro-2-(2-t-butylidemethylsilyloxyethyl)-3-oxo-
6-trifluoromethyl-2H-1,4-benzoxazine

Prepared from intermediate 10353-184-B (Reference Example 18) by method E in 90% yield, as a white solid, MS (Cl) 376 (MH⁺); IR (KBr) 3027, 15 3076, 2956, 2931, 2883, 2859, 1698, 1615, 1495, 1390, 1335, 1257, 1222, 1164, 1125, 1095, 1069, 956, 833, 777 cm⁻¹; ¹H NMR (CDCl₃) δ 8.59 (br s, 1H), 7.25, (m, 1H), 7.06 (m, 2H), 4.85 (dd, J = 9.2, 3.8 Hz, 1H), 3.85 (m, 2H), 2.23 (m, 1H), 2.02 (m, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). Calc'd for C₁₇H₂₄F₃NO₃Si: C 54.38, H 6.44, N 3.73. Found: C 54.34, H 6.45, N 3.73. 20 HRMS Calc'd for C₁₇H₂₄F₃NO₃Si (MH⁺): 376.1556. Found: 376.1570.

Reference Example 30

Intermediate 10353-188-A

25 3,4-Dihydro-2-(2-t-butylidemethylsilyloxyethyl)-3-oxo-
2H-pyrido[2,3-b]-1,4-oxazine

Prepared from 3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-pyrido[2,3-b]-1,4-oxazine by method E in 91% yield as off-white flakes MS (Cl) 309 (MH⁺); IR (KBr) 3053, 2955, 2884, 2857, 1699, 1610, 1510, 1463, 1375, 1357, 1278, 1256, 1092, 836, 775 cm⁻¹; ¹H NMR (CDCl₃) δ 10.40 (br s, 1H), 8.04 (dd, J = 5.4, 1.4 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.00 (dd, J = 7.7, 5.4 Hz, 1H), 4.83 (dd, J = 9.5, 4.1 Hz, 1H), 3.84 (m, 2H), 2.25 (m, 1H), 2.03 (m, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). HRMS Calc'd for C₁₅H₂₄N₂O₃Si (MH⁺): 35 309.1634. Found: 309.1608.

Reference Example 31

Intermediate 11653-23

2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-7-nitro-3-oxo-
2H-1,4-benzoxazine

5

Prepared from intermediate 11653-29A (Reference Example 15) by method E and isolated by recrystallization from Et₂O/hexane, mp 152-157°C; MS (FAB) MH⁺ 353; IR (KBr) 3548, 3209, 3094, 2936, 2889, 1702, 1600, 1529, 1509, 1483, 1418, 1390, 1344, 1229, 1133, 1035 cm⁻¹; ¹H NMR (CDCl₃) δ 9.45 (br s, 1H), 7.95 (dd, 1H, J = 2.4, 8.6 Hz), 7.91 (d, 1H, J = 2.3 Hz), 6.98 (d, 1H, J = 8.6 Hz), 4.93 (dd, 1H, J = 3.9, 9.0 Hz), 3.90 (m, 2H), 2.28 (m, 1H), 2.04 (m, 1H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

Anal. Calc'd for C₁₆H₂₄N₂O₅Si: C 54.52, H 6.86, N 7.95. Found: C 54.14, H 6.64, N 8.18.

15

Reference Example 32

Intermediate 11653-33A

2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-
6-nitro-3-oxo-2H-1,4-benzoxazine

20

Prepared from intermediate 11653-20A (Reference Example 26) by method E in 92% yield, mp 121.5-124.5°C; MS (FAB) MH⁺ 353; IR (KBr) 3190, 3125, 3055, 2952, 2884, 2426, 1921, 1623, 1446, 1296, 1281, 1209, 1004, 925, 682, 512 cm⁻¹; ¹H NMR (CDCl₃) δ 7.10 (dd, 1H, J = 2.65, 8.79 Hz), 7.75 (d, 1H, J = 2.56 Hz), 6.96 (dd, 1H, J = 4.99, 8.68 Hz), 4.80 (dd, 1H, J = 3.88, 9.30 Hz), 3.78 (m, 2H), 2.18 (m, 1H), 1.95 (m, 1H), 0.82 (s, 9H), 0.01 (d, 6H, J = 3.51 Hz). Anal. Calc'd for C₁₆H₂₄N₂O₅: C 54.52, H 6.86, N 7.95. Found: C 54.18, H 6.51, N 8.29.

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Reference Example 33

Intermediate 11653-163-A1

2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-
6-fluoro-3-oxo-2H-1,4-benzoxazine

35 Prepared from intermediate 11653-156-A (Reference Example 27) by method E in 77% yield mp 84-86°C; MS (CI) MH⁺ 326; IR (KBr) 3101, 3066, 2951, 2931, 2893, 2857, 1692, 1622, 1518, 1499, 1469, 1386, 1292, 1248, 1108, 1006, 812 cm⁻¹; ¹H NMR (CDCl₃) δ 8.86 (br s, 1H), 6.92 (dd, 1H, J =

4.9, 8.8 Hz), 6.67 (m, 1H), 6.60 (dd, 1H, $J = 2.9, 8.5$ Hz), 4.73 (dd, 1H, $J = 3.7, 9.5$ Hz), 3.91-3.78 (m, 2H), 2.26 (m, 1H), 1.98 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). Anal. Calc'd for $C_{16}H_{24}FNO_3Si$: C 59.05, H 7.43, N 4.30. Found: C 59.01, H 7.54, N 4.16.

5

Reference Example 34

Intermediate 11578-31

**2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-
5-methyl-3-oxo-2*H*-1,4-benzoxazine**

10

Prepared from 11578-28 (Reference Example 19) by Method E and isolated directly from the reaction mixture in 24% yield as a white solid, by adding water and collecting the precipitate, mp 90-92°C; IR (KBr) 2953, 2927, 2855, 1693, 1502, 1482, 1390, 1360, 1250, 1119, 1093, 959, 837, 780, 769 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.92-2.03 (m, 1H), 2.17-2.26 (m, 1H), 2.26 (s, 3H), 3.78-3.93 (m, 2H), 4.72 (dd, $J = 3.7, 9.7$ Hz, 1H), 6.81-6.92 (m, 3H), 8.04 (br s, 1H); Anal. Calc'd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47; N, 4.36. Found: C, 63.50; H, 8.53; N, 4.24.

20

Reference Example 35

Intermediate 11578-70

**2-(2-*tert*-Butyldimethylsiloxyethyl)-6-chloro-
3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine**

25

Prepared from 11578-68 (Reference Example 20) by Method E using 1 eq of imidazole and *t*-butyldimethylsilylchloride and isolated in 44% yield as a white solid after trituration with hexane, mp 86-89°C; MH^+ at $m/z = 342$; IR (KBr) 2955, 2928, 2881, 2857, 1700, 1496, 1400, 1360, 1231, 1124, 1094, 954, 834 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H),

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1.96-2.05 (m, 1H), 2.16-2.24 (m, 1H), 3.81-3.89 (m, 2H), 4.76 (dd, $J = 9.4, 3.7$ Hz, 1H), 6.83 (d, $J = 2$ Hz, 1H), 6.89-6.98 (m, 2H), 8.80 (br s, 1H). Anal. Calc'd for $C_{16}H_{24}ClNO_3Si$: C, 56.21; H, 7.08; N, 4.10. Found: C, 56.59; H, 7.17; N, 4.04.

35

Reference Example 36

Intermediate 11578-44

2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-
7-fluoro-3-oxo-2*H*-1,4-benzoxazine

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Prepared from 11578-42 (Reference Example 23) by Method E and isolated directly from the reaction mixture in 80% yield as a white solid, by adding water and collecting the precipitate, mp 100-102°C; IR (KBr) 2958, 2928, 2888, 2854, 1697, 1667, 1517, 1428, 1367, 1252, 1150, 1112, 1084, 833, 779 cm⁻¹; ¹H NMR (CDCl₃) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.96-2.05 (m, 1H), 2.16-2.27 (m, 1H), 3.80-3.91 (m, 2H), 4.77 (dd, J = 9.5, 3.8), 6.64-6.80 (m, 3H), 9.05 (br s, 1H); Anal. Calc'd for C₁₆H₂₄FNO₃Si: C, 59.05; H, 7.43; N, 4.30. Found: C, 58.98; H, 7.39; N, 4.27.

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Reference Example 37

Intermediate 11578-30

2-(2-*tert*-Butyldimethylsiloxyethyl)-6,8-dichloro-
3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

20

Prepared from 11578-22 (Reference Example 25) by Method E and isolated directly from the reaction mixture in 90% yield as a white solid, by adding water and collecting the precipitate, mp 118-120°C; IR (KBr) 2954, 2931, 2885, 2857, 1702, 1480, 1404, 1254, 1085, 838, 778 cm⁻¹; ¹H NMR (CDCl₃) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.90 (s, 9H), 1.94-2.03 (m, 1H), 2.15-2.21 (m, 1H), 3.77-3.89 (m, 1H), 3.93 (td, J = 9.7, 4.4 Hz, 1H), 4.89 (dd, J = 9.8, 3.5 Hz, 1H), 6.78 (d, J = 2.3 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 9.39 (br s, 1H); Anal. Calc'd for C₁₆H₂₃Cl₂NO₃Si: C, 51.06; H, 6.16; N, 3.72. Found: C, 50.72; H, 5.87; N, 3.82.

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Reference Example 38

Intermediate 11578-77-Precursor

2-(2-*tert*-Butyldimethylsiloxyethyl)-6-carbomethoxy
3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

35

Prepared from intermediate 11578-72 (Reference Example 21) by Method E in 80% yield. The crude product was used without purification, MH⁺ at m/z = 366.

Reference Example 39

Intermediate 12168-10-1

**4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-6-methyl-
2H-1,4-benzoxazine**

5

Prepared in two steps beginning from intermediate 12168-5-1 (Reference Example 28).

Method F: A solution of the silylated alcohol (2.17 g, 1 eq) in DMF (20 ml),
10 was treated with NaH (60% oil dispersion, 0.27 mg, 1eq) in one portion and
stirred at room temperature in an nitrogen atmosphere for 20 min, followed
by addition of 3-chlorobenzyl bromide (0.89 ml, 1eq). After 14h, the crude
reaction mixture was poured into cold water and extracted with EtOAc. The
combined organic extract was washed with brine and concentrated under
15 vacuum. The crude product was carried on to the next step without further
purification.

Method G: The product from Method F was dissolved in THF (15 ml) and tetrabutylammonium fluoride (1M solution in THF, 13 ml, 2 eq) was added. After stirring at room temperature for 8 h, the reaction mixture was concentrated under vacuum. The crude product was subjected to flash chromatography, eluting with EtOAc, and additionally purified by trituration with hot hexanes to afford the product in 93% overall yield, as a white solid, mp 75-78°C; MS (Cl) 332 (MH⁺); IR (KBr) 3501, 3451, 3062, 1969, 2937, 2874, 1660, 1610, 1598, 1575, 1513, 1473, 1432, 1387, 1321, 1280, 1258, 1106, 1067, 1061, 934, 775, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 7.27 (m, 3H), 7.17 (m, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 6.63 (s, 1H), 5.17 (d, *J* = 16.3 Hz, 1H), 5.08 (d, *J* = 16.3 Hz, 1H), 4.80 (dd, *J* = 7.6, 5.5 Hz, 1H), 3.92 (apparent q, *J* = 5.8 Hz, 2H), 2.29-2.17 (m, 3H), 2.23 (s, 3H). HRMS Calc'd for C₁₈H₁₈CINO₃ (MH⁺): 332.1053. Found: 332.1041.

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Reference Example 40

Intermediate 10353-191-1

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-6-methyl-2H-pyrido[2,3-b]-1,4-oxazine

35

Prepared from intermediate 10353-188-A (Reference Example 40) by methods F and G, alkylating with 3-chlorobenzyl bromide, in 69% overall yield as an off-white powder mp 80-81°C; MS (Cl) 319 (MH^+); IR (KBr) 3525,

3446, 2928, 2874, 1667, 1600, 1574, 1465, 1411, 1362, 1325, 1285, 1230,
 1205, 1121, 1096, 1064, 797, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 8.04 (dd, J = 4.8,
 1.5 Hz, 1H), 7.42 (s, 1H), 7.37-7.18 (m, 4H), 6.96 (dd, J = 7.9, 4.8 Hz, 1H),
 5.31 (s, 2H), 4.85 (dd, J = 7.5, 5.4 Hz, 1H), 3.90 (m, 2H), 2.35-2.16 (m, 2H),
 5 2.04 (t, 5.6 Hz, 1H). HRMS Calc'd for C₁₆H₁₅CIN₂O₃ (MH⁺): 319.0849.
 Found: 319.0857.

Reference Example 41

Intermediate 10353-28-1

10 4-(4-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
 3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
 benzoxazine by methods F and G, alkylating with 4-chlorobenzyl chloride, in
 15 63% overall yield as a white solid mp 86-88°C; MS (Cl) 300 (MH⁺ - H₂O); IR
 (KBr) 3496, 2977, 2890, 1656, 1607, 1501, 1466, 1401, 1297, 1250, 1088,
 1061, 1018, 795, 747 cm⁻¹; ¹H NMR (CDCl₃) δ 7.28 (d, J = 8.5 Hz, 2H), 7.18
 (d, J = 8.5 Hz, 2H), 7.05-6.87 (m, 3H), 6.83 (d, J = 8.0 Hz, 1H), 5.12 (s, 2H),
 4.83 (dd, J = 7.5, 5.5 Hz, 1H), 3.92 (apparent t, J = 5.7 Hz, 2H), 2.38-2.15 (m,
 20 3H). Calc'd for C₁₇H₁₆CINO₃: C 64.26, H 5.08, N 4.41. Found: C 64.01, H
 5.08, N 4.37.

Reference Example 42

Intermediate 9086-189-1

25 4-(2-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
 3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
 benzoxazine by methods F and G, alkylating with 2-chlorobenzyl chloride, in
 30 65% overall yield as white powder mp 90-91.5°C; MS (Cl) 318 (MH⁺ - H₂O);
 IR (KBr) 3482, 2935, 2881, 1663, 1607, 1594, 1505, 1466, 1443, 1407,
 1320, 1306, 1283, 1252, 1063, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42 (dd, J =
 7.6, 1.5 Hz, 1H), 7.30-7.13 (m, 2H), 7.08-9.88 (m, 4H), 6.73 (dd, J = 7.9, 1.3
 Hz, 1H), 5.25 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 17.3 Hz, 1H), 4.88 (dd, J = 7.5,
 35 5.5 Hz, 1H), 3.95 (apparent q, J = 5.9 Hz, 2H), 2.40-2.20 (m, 2H), 2.19 (t, J =
 5.9 Hz, 1H). Anal. Calc'd for C₁₇H₁₆CINO₃: C 64.26, H 5.08, N 4.41. Found:
 C 64.41, H 5.00, N 4.47.

Reference Example 43

Intermediate 12168-25-1

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-6-methoxy
2H-1,4-benzoxazine

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Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-6-methoxy-3-oxo-2H-1,4-benzoxazine by methods F and G, alkylating with 3-chlorobenzyl bromide, in 80% overall yield. Isolated by crystallization from EtOH/water to afford a white powder, MS (Cl) 348 (MH⁺); IR (KBr) 3501, 3053, 3021, 2959, 2933, 2876, 2838, 1664, 1618, 1600, 1575, 1512, 1466, 1445, 1435, 1390, 1361, 1337, 1313, 1272, 1237, 1201, 1173, 1107, 1078, 1049, 1030 cm⁻¹; ¹H NMR (CDCl₃) δ 7.27-7.20 (m, 3H), 7.13 (m, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.52 (dd, J = 9.1, 2.7 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 5.12 (d, J = 16.2 Hz, 1H), 4.79 (dd, J = 8.2, 5.4 Hz, 1H), 3.92 (m, 2H), 3.68 (s, 3H), 3.39-2.16 (m, 2H), 2.17 (t, J = 5.9 Hz, 1H). Anal. Calc'd for C₁₈H₁₈CINO₄ · 0.25 H₂O: C 61.37, H 5.29, N 3.98. Found: C 61.35, H 5.14, N 3.95.

Reference Example 44

Intermediate 11578-41

20 4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-
6-phenyl-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-6-phenyl-2H-1,4-benzoxazine by Methods F and G, alkylating with 3-chlorobenzyl bromide, to afford a white crystalline solid in 27% overall yield, mp 119-121°C; IR (KBr) 3517, 1659, 1487, 1435, 1387, 1282, 1260, 1060, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 2.22-2.38 (m, 3H), 3.95 (v br s, 2H), 4.90 (dd, J = 7.6, 5.5 Hz, 1H), 5.18 (ABq, J_{AB} = 17.1 Hz, 2H), 7.04 (d, J = 1.9 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.15-7.42 (m, 10H); MH⁺ at m/z = 394; Anal. Calc'd for C₂₃H₂₀CINO₃: C, 70.14; H, 5.12; N, 3.56. Found: C, 70.10; H, 5.11; N, 3.51.

Reference Example 45

Intermediate 10508-24-A

35 4-(3-Fluorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine by Methods F and G, alkylating with 3-fluorobenzyl chloride, in 49% overall yield and isolated as a gummy solid; IR (KBr) 3425, 1683, 1501, 1401, 1252, 1061, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 2.16-2.38 (m, 3H), 3.92 (t, J = 5.8 Hz, 2H), 4.85 (dd, J = 7.6, 5.5 Hz, 1H), 5.14 (s, 2H), 6.82-6.85 (m, 1H), 6.90-7.08 (m, 6H), 7.26-7.33 (m, 1H); MH⁺ at m/z = 302; Anal. Calc'd for C₁₇H₁₆FNO₃: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.48; H, 5.34; N, 4.57.

Reference Example 46

10

Intermediate 10840-33

3,4-Dihydro-2-(2-hydroxyethyl)-4-(4-methylbenzyl)-3-oxo-2*H*-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine by Methods F and G alkylating with 4-methylbenzyl chloride, in 50% overall yield. This material was crystallized from ether to afford a white solid, mp 92-94°C; IR (KBr) 3496, 1659, 1503, 1405, 1304, 1283, 1248, 1063, 801 cm⁻¹; ¹H NMR (CDCl₃) δ 2.18-2.36 (m, 5H), 3.91 (q, J = 5.7, 2H), 4.83 (dd, J = 7.4, 5.7, 1H), .5.12 (s, 2H), 6.90-7.00 (m, 4H), 7.13 (s, 4H); MH⁺ at m/z = 298; Anal. Calc'd for C₁₈H₁₉NO₃: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.71; H, 6.48; N, 4.65.

Reference Example 47

Intermediate 10508-19

25

3,4-Dihydro-2-(2-hydroxyethyl)-4-(4-methoxybenzyl)-3-oxo-2*H*-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine by Methods F and G, alkylating with 4-methoxybenzyl chloride, in 48% overall yield after flash chromatography eluting with EtOAc/hexane, mp 80-82°C; IR (KBr) 3496, 1660, 1515, 1501, 1412, 1250, 1057, 754 cm⁻¹; ¹H NMR (CDCl₃) δ 2.00 (v br s, 1H), 2.16-2.37 (m, 2H), 3.77 (s, 3H), 3.91 (t, J = 6.1 Hz, 2H), 4.82 (dd, J = 7.5, 5.6 Hz, 1H), 5.09 (s, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.91-7.00 (m, 4H), 7.18 (d, J = 8.7 Hz, 2H); MH⁺ at m/z = 314; Anal. Calc'd for C₁₈H₁₉NO₄: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.22; H, 6.10; N, 4.35.

Reference Example 48

Intermediate 10005-181-1

4-(3,5-Dichlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine

5

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with 3,5-dichlorobenzyl chloride, in 89% overall yield. A sample was crystallized from CH₂Cl₂/hexane/ether to afford a white solid, mp 104-106°C; IR (KBr) 3525, 1680, 1570, 1505, 1398, 1063, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 1.92 (br s, 1H), 2.17-2.37 (m, 2H), 3.93 (t, J = 5.7 Hz, 2H), 4.87 (q, J = 5.4 Hz, 1H), 5.13 (ABq, J_{AB} = 16.3 Hz, 2H), 6.78 (d, J = 7.3 Hz, 1H), 6.93-7.05 (m, 2H), 7.12 (br d, J = 1.7 Hz, 2H), 7.26-7.28 (m, 2H); Anal. Calc'd for C₁₇H₁₅Cl₂NO₃: C, 57.97; H, 4.29; N, 3.98. Found: C, 57.96; H, 4.17; N, 3.87.

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Reference Example 49

Intermediate 11578-71

6-Chloro-4-(3-chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine

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Prepared from intermediate 11578-70 (Reference Example 35) by Methods F and G, alkylating with 3-chlorobenzyl bromide, and isolated in 43% overall yield as a white solid, mp 90-92°C; IR (KBr) 3499, 1663, 1601, 1497, 1433, 1386, 1324, 1267, 1091, 1050, 933, 783 cm⁻¹; ¹H NMR (CDCl₃) δ 2.05 (br s, 1H), 2.18-2.30 (m, 2H), 3.89-3.97 (m, 2H), 4.86 (dd, J = 7.7, 5.5 Hz, 1H), 5.1 (s, 2H), 6.81 (s, 1H), 6.96 (d, J = 1.4 Hz, 2H), 7.12-7.30 (m, 4H); MH⁺ at m/z = 352; Anal. Calc'd for C₁₇H₁₅Cl₂NO₃: C, 57.95; H, 4.29; N, 3.98. Found: C, 58.26; H, 4.32; N, 3.89.

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Reference Example 50

Intermediate 11578-56

4-(3-Chlorobenzyl)-6-trifluoromethyl-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine 0.2 Hydrate

25

Prepared from intermediate 12168-8-1 (Reference Example 29) by methods F and G, alkylating with 3-chlorobenzyl bromide, in 96% yield as a white crystalline solid, mp 92-94°C; IR (KBr) 3520, 1671, 1454, 1330, 1299, 1269, 1120, 868, 712 cm⁻¹; ¹H NMR (CDCl₃) δ 2.20-2.40 (m, 2H), 3.92 (t, J = 6.3

Hz, 2H), 4.93 (t, J = 7.6 Hz, 1H), 5.14 (s, 2H), 7.07-7.16 (m, 3H), 7.23-7.30 (m, 4H); MH⁺ at m/z = 386; Anal. Calc'd for C₁₈H₁₅ClF₃NO₃·0.2H₂O: C, 55.52; H, 3.99; N, 3.60. Found: C, 55.49; H, 3.77; N, 3.53.

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Reference Example 51

Intermediate 11578-77

**6-Carbomethoxy-4-(3-chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine**

- 10 Prepared from 2-(2-*tert*-butyldimethylsiloxyethyl)-6-carbomethoxy-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with 3-chlorobenzyl bromide, in 70% overall yield as a white solid, after trituration with hexane, IR (KBr) 3468, 2952, 1688, 1452, 1285, 1260, 765 cm⁻¹; ¹H NMR (CDCl₃) δ 1.61 (br s, 1H plus HDO), 2.17-2.39 (m, 2H), 3.86 (s, 3H), 3.93 (t, J = 5.7 Hz, 2H), 4.94 (dd, J = 7.6, 5.5 Hz, 1H), 5.16 (s, 2H), 7.04 (d, J = 8.4, 1H), 7.15-7.33 (m, 4H), 7.59 (d, J = 1.8 Hz, 1H), 7.71 (dd, J = 8.4, 1.8 Hz, 1H); MH⁺ at m/z = 376; Anal. Calc'd for C₁₉H₁₈ClNO₅·0.1H₂O: C, 60.44; H, 4.86; N, 3.71. Found: C, 60.26; H, 4.60; N, 3.58.
- 15

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Reference Example 52

Intermediate 11578-47

**4-(3-Chlorobenzyl)-3,4-dihydro-7-fluoro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine**

- 25 Prepared from intermediate 11578-44 (Reference Example 36) by Methods F and G, alkylating with 3-chlorobenzyl bromide, in 76% overall yield. This material was isolated as an off-white solid, mp 79-82°C; IR (KBr) 3487, 1662, 1508, 1412, 1320, 1155, 1115, 1053, 854, 799 cm⁻¹; ¹H NMR (CDCl₃) δ 2.10 (t, J = 4.3 Hz, 1H), 2.18-2.40 (m, 2H), 3.92 (q, J = 6.0 Hz, 2H), 4.88 (t, J = 5.5 Hz, 1H), 5.10 (ABq, J_{AB} = 15.4 Hz, 2H), 6.64 (td, J = 7.9, 2.7 Hz, 1H), 6.72-6.79 (m, 2H), 7.11 (br s, 1H), 7.22-7.28 (m, 3H plus CHCl₃); MH⁺ at m/z = 336; Anal. Calc'd for C₁₇H₁₅ClFNO₃: C, 60.81; H, 4.50; N, 4.17. Found: C, 60.74; H, 4.69; N, 4.28.
- 30

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Reference Example 53

Intermediate 11578-113

**7-Fluoro-3,4-dihydro-4-(3-fluorobenzyl)-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benz xazine**

Prepared from intermediate 11578-44 (Reference Example 36) by Methods F and G, alkylating with 3-fluorobenzyl chloride, to afford a white solid in 67% yield, mp 78-79°C; IR (KBr) 3497, 1661, 1509, 1415, 1252, 1159, 1119,

- 5 1057, 937, 857, 801 cm⁻¹; ¹H NMR (CDCl₃) δ 2.11 (t, J = 5.1 Hz, 1H), 2.17-2.39 (m, 2H), 3.92 (q, J = 5.5 Hz, 2H), 4.87 (dd, J = 7.6, 5.5 Hz, 1H), 5.13 (s, 2H), 6.64 (td, J = 8.0, 2.7 Hz, 1H), 6.73-6.79 (m, 2H), 6.94 (t, J = 8.5 Hz, 2H), 7.01 (s, J = 7.7 Hz, 1H), 7.27-7.35 (m, 1H); MH⁺ at m/z = 320; Anal. Calc'd for C₁₇H₁₅F₂NO₃: C, 63.95; H, 4.74; N, 4.39. Found: C, 63.91; H, 4.70; N, 4.30.

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Reference Example 54

Intermediate 11578-114

7-Fluoro-3,4-dihydro-2-(2-hydroxyethyl)-4-(2-nitrobenzyl)-
3-oxo-2H-1,4-benzoxazine

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- Prepared from intermediate 11578-44 (Reference Example 36) by Methods F and G, alkylating with 2-nitrobenzyl chloride, to afford a white solid after column chromatography, eluting with ether, in 76% yield. A portion of this material was crystallized from hexane, mp 123-124°C; IR (KBr) 3510, 1655, 20 1527, 1509, 1357, 1157, 1127, 1063, 801 cm⁻¹; ¹H NMR (CDCl₃) δ 2.01 (t, J = 5.1 Hz, 1H), 2.22-2.38 (m, 2H), 3.93 (q, J = 5.6 Hz, 2H), 4.92 (dd, J = 7.54, 5.63 Hz, 1H), 5.23 (ABq, J_{AB} = 16.5 Hz, 2H), 6.63-6.75 (m, 2H), 6.80 (dd, J = 8.7, 2.6 Hz, 1H), 7.51-7.60 (m, 2H), 8.12 (s, 1H), 8.15 (d, J = 7.1 Hz, 1H); MH⁺ at m/z = 347; Anal. Calc'd for C₁₇H₁₅FN₂O₅: C, 58.96; H, 4.37; N, 8.09. 25 Found: C, 58.81; H, 4.37; N, 8.01.

Reference Example 55

Intermediate 11578-52

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-7-methyl-
3-oxo-2H-1,4-benzoxazine

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- Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-7-methyl-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with 3-chlorobenzyl bromide, in 76% yield as a white solid after crystallization from ether/hexane, 35 mp 72-74°C; IR (KBr) 3418, 1679, 1512, 1402, 1292, 1061, 763 cm⁻¹; ¹H NMR (CDCl₃) δ 2.20-2.36 (m, 3H), 2.27 (s, 3H), 3.92 (q, J = 5.6 Hz, 2H), 4.83 (dd, J = 7.6, 5.5 Hz, 1H), 5.10 (ABq, J_{AB} = 17.0 Hz, 2H), 6.68-6.75 (m, 2H), 6.84 (s, 1H), 7.10-7.14 (m, 1H), 7.22-7.29 (m, 3H); MH⁺ at m/z = 332; Anal.

Calc'd for C₁₈H₁₈CINO₃·0.2H₂O: C, 64.46; H, 5.53; N, 4.18. Found: C, 64.48; H, 5.51; N, 4.06.

Reference Example 56

5

Intermediate 11578-33

4-(3-Chlorobenzyl)-6,8-dichloro-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2*H*-1,4-benzoxazine

Prepared from intermediate 11578-30 (Reference Example 37) by Methods
10 F and G, alkylating with 3-chlorobenzyl bromide, in 80% yield. This material
was isolated as a white foam after flash chromatography using ether/CH₂Cl₂
(1/4); IR (KBr) 3430, 1694, 1592, 1480, 1434, 1380, 1285, 1059, 933, 843,
755 cm⁻¹; ¹H NMR (CDCl₃) 2.00 (t, J = 5.4 Hz, 1H), 2.15-2.40 (m, 2H), 3.92-
4.03 (m, 2H), 4.97 (dd, J = 8.8, 4.7 Hz, 1H), 5.09 (s, 2H), 6.72 (d, J = 2.3 Hz,
15 1H), 7.08 (d, J = 2.2 Hz, 2H), 7.20 (s, 1H), 7.26-7.30 (m, 2H plus CHCl₃);
Anal. Calc'd for C₁₇H₁₄Cl₃NO₃: C, 52.81; H, 3.65; N, 3.62. Found: C, 52.90;
H, 3.73; N, 3.46.

Reference Example 57

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Intermediate 10840-18

3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-4-(2-picoly)-2*H*-1,4-benzoxazine

2-*(2-tert-Butyldimethylsiloxyethyl)*-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine
was alkylated with 2-chloromethylpyridine by method F and the crude
25 product was deprotected by method H without purification.
Method H: The *t*-butyldimethylsiloxy intermediate was dissolved in
methanol and an excess of 6N HCl. The solution was stirred at room
temperature 1h and then concentrated under vacuum. The aqueous residue
was extracted with dichloromethane and the combined extract was washed
30 with brine and dried over Na₂SO₄. Removal of solvent produced the crud
product which was purified by flash chromatography in 42% yield and was
isolated as a white solid after crystallization from ether/hexane, mp 108-
111°C; IR (KBr) 2881, 1675, 1505, 1401, 1279, 1115, 1070, 749 cm⁻¹; ¹H
NMR (CDCl₃) δ 2.18-2.38 (m, 2H), 2.44 (br s, 1H), 3.92 (br d, J = 3.8 Hz, 2H),
35 4.86 (dd, J = 7.2, 5.8 Hz, 1H), 5.27 (ABq, J_{AB} = 16.3 Hz, 2H), 6.89-7.03 (m,
4H), 7.17-7.24 (m, 2H), 7.64 (td, J = 7.7, 1.7 Hz, 1H), 8.56 (br d, J = 4.3 Hz,
1H); MH⁺ at m/z = 285; Anal. Calc'd for C₁₆H₁₆N₂O₃: C, 67.59; H, 5.67; N,
9.85. Found: C, 67.55; H, 5.83; N, 9.83.

Reference Example 58

Intermediate 10840-22

3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-4-(4-picoly)-2H-1,4-benzoxazine

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Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and H, alkylating with 4-chloromethylpyridine, in 12% yield and isolated as a beige solid, mp 153-154°C; IR (KBr) 3204, 1679, 1505, 1407, 1283, 1256, 1077, 1065, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 2.18-2.38 (m, 3H), 3.93 (br q, J = 3.9 Hz, 2H), 4.88 (dd, J = 7.7, 5.4 Hz, 1H), 5.15 (s, 2H), 6.73 (d, J = 7.6 Hz, 1H), 6.92 (td, J = 6.7, 3.2 Hz, 1H), 6.98-7.06 (m, 2H), 7.15 (d, J = 5.9 Hz, 2H), 8.56 (dd, J = 4.5, 1.5 Hz, 2H); MH⁺ at m/z = 285; Anal. Calc'd for C₁₆H₁₆N₂O₃: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.67; H, 5.78; N, 9.79.

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Reference Example 59

Intermediate 11578-99

3,4-Dihydro-2-(2-hydroxyethyl)-4-(4-phenylbenzyl)-3-oxo-2H-1,4-benzoxazine

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Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with 4-phenylbenzyl chloride, in 98% yield as a yellow crystalline solid, mp 110-113°C; IR (KBr) 3350, 1683, 1500, 1400, 1304, 1275, 1247, 1051, 908, 758 cm⁻¹; ¹H NMR (CDCl₃) δ 2.21-2.38 (m, 2H), 3.94 (q, J = 5.48 Hz, 2H), 4.87 (dd, J = 7.5, 5.61 Hz, 1H), 5.20 (ABq, J_{AB} = 17.1 Hz, 2H), 6.93-7.04 (m, 4H), 7.30-7.40 (m, 3H), 7.43 (t, J = 7.0 Hz, 2H), 7.55 (d, J = 8.1 Hz, 4H); MH⁺ at m/z = 360; Anal. Calc'd for C₂₃H₂₁NO₃: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.61; H, 5.88; N, 3.74.

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4-Phenylbenzyl chloride was prepared by treating a CH₂Cl₂ solution of the corresponding alcohol (1 eq) with methanesulfonyl chloride (1.1 eq) and TEA (1.1 eq) at 0°C. This solution was stirred for 16 h, treated with 3N HCl and the organic layer was isolated. After drying, the solvent was evaporated to afford the 4-phenylbenzyl chloride in 64% yield, MH⁺ at m/z = 202.

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Reference Example 60

Intermediate 10840-185

3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-4-pentyl-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with 1-chloropentane in 32% yield and isolated as a colorless oil; IR (KBr) 3424, 2956, 2932, 1680, 1500, 1272, 1062, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 0.91 (t, J = 6.8 Hz, 3H), 1.31-1.38 (m, 4H), 1.66 (br t, J = 5.5 Hz, 2H), 2.08-2.29 (m, 2H), 2.59 (br s, 1H), 3.87-3.94 (m, 2H), 4.69 (dd, J = 7.3, 5.8 Hz, 1H), 6.92-7.08 (m, 4H); Anal. Calc'd for C₁₅H₂₁NO₃: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.10; H, 7.88; N, 5.32.

Reference Example 61

10

Intermediate 11653-180

3,4-Dihydro-2-(2-hydroxyethyl)-4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

The intermediate silyl protected alcohol was prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Method F, alkylating with 3-nitrobenzyl chloride. Deprotection to the indicated product was carried out by method I.

Method I: The TBDMS-protected benzoxazine (3.1 mmol) was stirred into a milky mixture with AcOH (12 mL), THF (2 mL) and H₂O (5 mL). This mixture was stirred for 18 h to give a clear solution. The addition of water gave a white solid precipitate which was filtered and dried in vacuo at 80 °C: mp 103-104°C; MS (CI) MH⁺329; IR (KBr) 3490, 3087, 2947, 2879, 1685, 1663, 1607, 1593, 1466, 1280, 1168, 976 cm⁻¹; ¹H NMR (CDCl₃) δ 8.15 (s, 1H), 8.13 (s, 1H), 7.54 (m, 2H), 7.04 (m, 2H), 6.95 (m, 1H), 6.79 (d, 1H, J = 7.6Hz), 5.28 (d, 1H, J = 16.5Hz), 5.21 (d, 1H, J = 16.5Hz), 4.90 (dd, 1H, J = 5.5, 7.6Hz), 3.93 (m, 2H), 2.29 (m, 2H), 2.13 (t, 1H, J = 5.6Hz). Anal. Calc'd for C₁₇H₁₆N₂O₅: C 62.19, H 4.91, N 8.53. Found: C 61.99, H 4.91, N 8.43.

Reference Example 62

Intermediate 12279-11

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3,4-Dihydro-2-(2-hydroxyethyl)-7-nitro-4-(4-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

Prepared from intermediate 11653-23 (Reference Example 31) by methods F and I and isolated as a yellow-orange solid in 42% yield, mp 100-104°C; MS (CI) MH⁺ 374; IR (KBr) 3395, 3113, 3089, 2939, 1683, 1598, 1432, 1395, 1142, 991, 914, 800, 544, 455 cm⁻¹; ¹H NMR (CDCl₃) δ 8.23 (d, 2H, J = 8.70Hz), 7.92 (d, 1H, J = 2.42Hz), 7.85 (dd, 1H, J = 8.85, 2.54Hz), 7.41 (d, 2H, J = 8.60Hz), 6.85 (d, 1H, J = 8.93), 5.30 (d, 2H, J = 4.56Hz), 5.01 (dd, 1H,

J = 7.76, 5.11Hz), 3.96 (t, 2H, *J* = 6.45Hz), 2.30 (m, 2H), 1.79 (br.s, 1H). Anal. Calc'd for C₁₇H₁₅N₃O₇ · 0.7 H₂O: C 52.91, H 4.28, N 10.89. Found: C 53.17, H 4.36, N 10.53.

5

Reference Example 63

Intermediate 12279-18-A

3,4-Dihydro-2-(2-hydroxyethyl)-7-methoxy-4-(3-nitrobenzyl)-
3-oxo-2*H*-1,4-benzoxazine

- 10 Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-7-methoxy-3-oxo-2*H*-1,4-benzoxazine by methods F and I, alkylating with 3-nitrobenzyl chloride, in 30% yield, mp 116-118°C; MS (Cl) MH⁺ 359; IR (KBr) 3306, 3086, 2926, 2872, 1628, 1595, 1476, 1309, 1290, 1255, 1087, 999, 713, 458 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.14 (s, 1H), 8.11 (s, 1H), 7.63 (m, 2H), 6.97 (d, 1H, *J* = 8.93Hz), 6.66 (d, 1H, *J* = 2.42Hz), 6.53 (d, 1H, *J* = 8.87Hz), 5.26 (s, 2H), 4.87 (dd, 1H, *J* = 8.98, 3.78Hz), 4.72 (t, 1H, *J* = 5.23Hz), 3.68 (s, 3H), 3.61 (m, 2H), 2.01 (m, 1H), 1.90 (m, 1H). Anal. Calc'd for C₁₈H₁₈N₂O₆: C 60.33 H 5.06, N 7.82. Found: C 59.96, H 5.08, N 7.62.
- 15

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Reference Example 64

Intermediate 12279-21

3,4-Dihydro-6-fluoro-2-(2-hydroxyethyl)-4-(3-nitrobenzyl)-
3-oxo-2*H*-1,4-benzoxazine

- 25 Prepared from intermediate 11653-163-A1 (Reference Example 33) by methods F and I, alkylating with 3-nitrobenzyl chloride, in 35% yield, mp 110-112°C; MS (Cl) MH⁺ 347; IR (KBr) 3483, 3077, 2945, 2872, 1620, 1603, 1453, 1297, 1210, 1098, 979, 791, 742, 685, 470 cm⁻¹; ¹H NMR (CDCl₃) δ 8.16 (d, 1H, *J* = 6.87Hz), 8.10 (s, 1H), 7.54 (m, 2H), 6.90 (dd, 1H, *J* = 3.73, 5.12Hz), 6.71 (m, 1H), 6.51 (dd, 1H, *J* = 9.35, 2.76Hz), 5.20 (d, 2H, *J* = 5.46Hz), 4.87 (dd, 1H, *J* = 7.60, 5.41Hz), 3.93 (t, 2H, *J* = 5.78Hz), 2.29 (m, 2H), 2.00 (m, 1H). Anal. Calc'd for C₁₇H₁₅FN₂O₅: C 58.96, H 4.37, N 8.09. Found: C 58.57, H 4.43, N 7.89.
- 30

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Reference Example 65

Intermediate 12279-13-A

4-(3-Aminobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2*H*-1,4-benzoxazine

- Prepared by dissolving the intermediate t-butyldimethylsiloxy compound from example 11653-180 (1.58 g, Reference Example 61) in ethanol (25 ml). Fe powder (1.3 g) was added with stirring, followed by conc. HCl (12 ml).
- 5 The reaction was stirred at room temperature for 16 hrs. The reaction was filtered directly into ice water, and extracted with EtOAc. The extract was washed with brine, and concentrated under vacuum. The resulting brown oil was rinsed in ether. After decanting the ether, the oil was scratched to produce the product as a light brown solid in 50% yield, mp 79°C-darkens,
- 10 85-90°C-melts; MS (Cl) MH⁺ 299; IR (KBr) 3470, 3373, 3215, 3031, 2930, 2877, 1657, 1605, 1590, 1465, 1441, 1356, 1251, 1183, 1165, 1101, 1016, 995, 898, 688, 560 cm⁻¹; ¹H NMR (CDCl₃) δ 7.10 (t, 1H, J = 7.70Hz), 7.10-6.20(v br.s, 2H), 6.98 (m, 2H), 6.93 (m, 2H), 6.63 (d, 1H, J = 7.8Hz), 6.56 (d, s, 2H, J = 8.6Hz), 5.10 (d, 1H, J = 16.0Hz), 5.00 (d, 1H, J = 16.0Hz), 4.83 (dd, 1H, J = 5.61, 7.45Hz), 3.91(q, 2H, J = 5.4Hz), 3.85-3.20(v br.s, 1H), 2.23 (m, 2H). Anal. Calc'd for C₁₇H₁₈N₂O₃ · 0.1 H₂O: C 68.03, H 6.11, N 9.33. Found: C 67.93, H 6.05, N 9.05.
- 15

Reference Example 66

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Intermediate 10488-22

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine

- Prepared by methods F and G, alkylating with 3-chlorobenzyl bromide, in 55 % yield. The product was isolated as an oil which could be crystallized from Et₂O/Hexane, mp 63-67°C; MS (Cl) MH⁺ 318; IR (KBr) 3477, 2927, 2863, 1688, 1599, 1576, 1503, 1466, 1217, 1109, 931, 903 cm⁻¹; ¹H NMR (CDCl₃) 7.26 (m, 3H), 7.12 (m, 1H), 7.01 (m, 2H), 6.94 (m, 1H), 6.82 (m, 1H), 5.15 (d, 1H, J = 16.3Hz), 5.08 (d, 1H, J = 16.2Hz), 4.85 (dd, 1H, J = 5.5, 7.6Hz), 3.92 (d, 2H, J = 4.9Hz), 2.39-2.14 (br. m, 3H). Anal. Calc'd for C₁₇H₁₆ClNO₃: C 64.26, H 5.08, N 4.44. Found: C 63.89, H 5.00, N 4.13.
- 25
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Reference Example 67

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Intermediate 11653-85-B-1

3,4-Dihydro-2-(2-hydroxyethyl)-7-nitro-4-(3-nitrobenzyl)-
3-oxo-2H-1,4-benzoxazine

Prepared from intermediate 11653-23 (Reference Example 31) by methods F and G, alkylating with 3-nitrobenzyl chloride, in 66% yield, mp 157-160°C; MS (Cl) MH⁺ 374; IR (KBr) 3592, 3433, 3087, 2926, 2892, 1671, 1598, 1525, 1482, 1433, 1219, 1168, 1097, 838 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.17
 5 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.83 (d, 1H, J = 2.5 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.58 (t, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 9.2 Hz), 5.40 (d, 1H, J = 16.5 Hz), 5.31 (d, 1H, J = 16.6), 5.07 (dd, 1H, J = 4.0, 9.0 Hz), 4.57 (t, 1H, J = 5.2 Hz), 3.80 (m, 2H), 2.23 (m, 1H), 2.10 (m, 1H). Anal. Calc'd for C₁₇H₁₅N₃O₇: C 54.69, H 4.05, N 11.26. Found: C 54.57, H 4.04, N 11.08.

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Reference Example 68

Intermediate 11653-58C

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-6-nitro-
 3-oxo-2H-benzoxazine

15

Prepared from intermediate 11653-33A (Reference Example 32) by methods F and G, alkylating with 3-chlorobenzyl bromide, in 77% yield, mp >38°C (dec); MS (Cl) MH⁺ 363; IR (KBr) 3855, 3745, 3423, 1686, 1590, 1522, 1448, 1389, 1343, 1267, 1056, 875, 778, 680 cm⁻¹; ¹H NMR (CDCl₃) δ 7.93
 20 (dd, 1H, J = 2.5, 8.8Hz), 7.78 (d, 1H, J = 2.5Hz), 7.30 (m, 3H), 7.19 (m, 1H), 7.10 (d, 1H, J = 8.8Hz), 5.20 (d, 1H, J = 16.3Hz), 5.14 (d, 1H, J = 16.2Hz), 5.03 (dd, 1H, J = 5.3, 7.6Hz), 3.93 (t, 2H, J = 6.2Hz), 2.41-2.19 (m, 2H), 1.71 (br s, 1H). Anal. Calc'd for C₁₇H₁₅Cl N₂O₅: C 56.29, H 4.17, N 7.72. Found: C 56.19, H 4.22, N 7.55.

25

Reference Example 69

Intermediate 11653-142

3,4-Dihydro-2-(2-hydroxyethyl)-7-nitro-4-(2-nitrobenzyl)-
 3-oxo-2H-1,4-benzoxazine

30

Prepared from intermediate 11653-23 (Reference Example 31) by methods F and I, alkylating with 2-nitrobenzyl chloride, in 52% yield, mp 139-143°C; MS (Cl) MH⁺ 374; IR (KBr) 3569, 3122, 3088, 2942, 2892, 1693, 1600, 1530, 1501, 1420, 1390, 1254, 1059, 888, 727 cm⁻¹; ¹H NMR (DMSO-d₆) δ
 35 8.24 (dd, 1H, J = 1.2, 8.0 Hz), 7.90 (d, 1H, J = 2.5Hz), 7.83 (dd, 1H, J = 2.6, 8.9 Hz), 7.62 (m, 2H), 7.20 (d, 2H, J = 8.9 Hz), 5.59 (d, 1H, J = 18.2 Hz), 5.49 (d, 1H, J = 18.2 Hz), 5.16 (dd, 1H, J = 4.4, 8.5 Hz), 4.79 (t, 1H, J = 5.2 Hz),

3.66 (m, 2H), 2.05 (m, 2H). Anal. Calc'd for C₁₇H₁₅N₃O₇: C 54.69, H 4.05, N 11.26. Found: C 54.81, H 4.03, N 11.07.

Reference Example 70

5

Intermediate 11653-44A

4-(2-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-6-nitro-3-oxo-2H-benzoxazine

Prepared from intermediate 11653-33A (Reference Example 32) by methods F and G, alkylating with 2-chlorobenzyl chloride, in 23% yield, mp 108-110°C; MS (Cl) MH⁺ 363; IR (KBr) 3520, 3092, 2984, 2938, 2889, 1906, 1775, 1588, 1474, 1446, 1316, 1253, 1185, 1127, 1112, 926, 680 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.94 (dd, 1H, J = 2.5, 8.8Hz), 7.62 (d, 1H, J = 2.5Hz), 7.56 (d, 1H, J = 7.6Hz), 7.31 (m, 3H), 7.15 (d, 1H, J = 7.3Hz), 5.25 (s, 2H), 5.16 (dd, 1H, J = 4.2, 8.5Hz), 4.78 (t, 1H, J = 5.2Hz), 3.63 (m, 2H), 2.09 (m, 2H). Anal. Calc'd for C₁₇H₁₅ClN₂O₅: C 56.29, H 4.17, N 7.72. Found: C 56.19, H 4.10, N 7.58.

Reference Example 71

20

Intermediate 11653-173

3,4-Dihydro-2-(2-hydroxyethyl)-4-(4-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by methods F and I, alkylating with 4-nitrobenzyl chloride, in 89% yield, mp 124-127°C; MS (Cl) MH⁺ 329; IR (KBr) 3498, 3076, 2930, 2863, 1656, 1605, 1500, 1466, 1302, 1279, 1184, 1126, 982, 613 cm⁻¹; ¹H NMR (CDCl₃) δ 8.20 (dd, 2H, J = 2.0, 6.9 Hz), 7.40 (d, 2H, J = 8.8 Hz), 7.03 (m, 2H), 6.93 (m, 1H), 6.75 (d, 1H, J = 7.6 Hz), 5.25 (s, 2H), 4.88 (dd, 1H, J = 5.4, 7.6 Hz), 3.93 (m, 2H), 2.38-2.17 (m, 2H), 2.10 (m, 1H). Anal. Calc'd for C₁₇H₁₆N₂O₅: C 62.19, H 4.91, N 8.54. Found: C 62.05, H 4.87, N 8.39.

Reference Example 72

Intermediate 11653-170-A2

35

4-Benzyl-3,4-dihydro-2-(2-hydroxyethyl)-7-nitro-3-oxo-2H-1,4-benzoxazine

Prepared from intermediate 11653-23 (Reference Example 31) by methods F and G, alkylating with benzyl bromide, in 98% yield, mp 102-105°C; MS (Cl) MH⁺ 329; IR (KBr) 3561, 3086, 3062, 2970, 2932, 2873, 1698, 1598, 1500, 1452, 1075, 985 cm⁻¹; ¹H NMR (CDCl₃) δ 7.88 (d, 1H, J = 2.5 Hz), 7.82 (dd, 1H, J = 2.5, 8.9 Hz), 7.34 (m, 3H), 7.23 (m, 2H), 6.96 (d, 1H, J = 8.9 Hz), 5.23 (d, 1H, J = 16.4 Hz), 5.17 (d, 1H, J = 16.4 Hz), 4.80 (dd, 1H, J = 5.1, 7.9 Hz), 3.94 (m, 2H), 2.34 (m, 1H), 2.28 (m, 1H), 1.98 (t, 1H, J = 5.5 Hz). Anal. Calc'd for C₁₇H₁₆N₂O₅: C 62.19, H 4.91, N 8.53. Found: C 61.81, H 4.63, N 8.36.

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Reference Example 73

Intermediate 11653-174-A

3,4-Dihydro-2-(2-hydroxyethyl)-4-(3-nitrobenzyl)-
3-oxo-2H-1,4-benzoxazine

15

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by methods F and I, alkylating with 2-nitrobenzyl chloride, in 43% yield, mp 128.5-130°C; MS (Cl) MH⁺ 329; IR (KBr) 3850, 3495, 3074, 2974, 2949, 2896, 1658, 1605, 1576, 1515, 1503, 1468, 1426, 1362, 1218, 1163, 902 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.20 (dd, 1H, J = 1.3, 8.1 Hz), 7.67 (t, 1H, J = 7.6 Hz), 7.56 (t, 1H, J = 7.0 Hz), 7.15 (d, 1H, J = 7.0 Hz), 7.08 (d, 1H, J = 7.7 Hz), 6.99 (m, 1H), 6.92 (d, 2H, J = 3.7 Hz), 5.49 (d, 1H, J = 18.2 Hz), 5.42 (d, 1H, J = 18.1 Hz), 4.94 (dd, 1H, J = 4.1, 9.0 Hz), 4.72 (t, 1H, J = 5.2 Hz), 3.63 (m, 2H), 2.00 (m, 2H). Anal. Calc'd for C₁₇H₁₆N₂O₅: C 62.19, H 4.91, N 8.53. Found: C 61.85, H 4.89, N 8.37.

Reference Example 74

Intermediate 10508-23-A

4-Benzyl-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazine

30

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with benzyl chloride, in 49% overall yield and crystallized from ether/hexane to produce a white solid, mp 83-85.5°C; IR (KBr) 3213, 1680, 1505, 1399, 1250, 1050, 753 cm⁻¹; ¹H NMR (CDCl₃) δ 2.17-2.38 (m, 3H), 3.92 (q, J = 5.7 Hz, 2H), 4.84 (dd, J = 7.5, 5.6 Hz, 1H), 5.16 (s, 2H), 6.86-7.03 (m, 4H), 7.21-7.37 (m, 5H); MH⁺ at m/z = 284; Anal. Calc'd for C₁₇H₁₇NO₃: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.08; H, 6.20; N, 4.87.

Reference Example 75

Intermediate 10508-25-A

3,4-Dihydro-2-(2-hydroxyethyl)-4-(2-methoxybenzyl)-

5

3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by methods F and G, alkylating with the methanesulfonate ester of 2-methoxybenzyl alcohol, in 47% overall yield as a light yellow gum
 10 after flash chromatography, eluting with EtOAc/hexanes, IR (Neat) 3436, 2941, 1583, 1683, 1501, 1466, 1403, 1281, 1246, 1113, 1052, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 2.18-2.36 (m, 2H), 2.39 (br t, J = 6.0 Hz, 1H), 3.90 (s, 3H), 3.92 (br q, J = 5.5 Hz, 2H), 4.85 (dd, J = 7.4, 5.7 Hz, 1H), 5.15 (s, 2H), 6.81-7.03 (m, 7H), 7.23 (td, J = 8.3, 1.7 Hz, 1H); MH⁺ at m/z = 314; Anal. Calc'd for
 15 C₁₈H₁₉NO₄·0.2 H₂O: C, 68.21; H, 6.17; N, 4.42. Found: C, 68.36; H, 6.18; N, 4.36.

Reference Example 76

Intermediate 10508-22-A

20 3,4-Dihydro-2-(2-hydroxyethyl)-4-(3-methoxybenzyl)-
 3-oxo-2H-1,4-benzoxazine

Prepared by Methods F and G, alkylating with 3-methoxybenzyl chloride, in 49% overall yield as a clear viscous gum, after flash chromatography eluting
 25 with 25-50% EtOAc in hexane, IR (Neat) 3433, 2941, 1683, 1583, 1501, 1466, 1403, 1262, 1152, 1052, 753 cm⁻¹; ¹H NMR (CDCl₃) δ 2.17-2.37 (m, 3H), 3.77 (s, 3H), 3.91 (br q, J = 5.3 Hz, 2H), 4.84 (dd, J = 7.5, 5.6 Hz, 1H), 5.12 (ABq, J_{AB} = 17 Hz, 2H), 6.76-7.03 (m, 7H), 7.24 (td, J = 7.6, 0.98 Hz, 1H); MH⁺ at m/z = 314; Anal. Calc'd for C₁₈H₁₉NO₄: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.54; H, 6.14; N, 4.33.

Reference Example 77

Intermediate 10508-82-A

35 4-(3-Benzylbenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
 3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by Methods F and G, alkylating with the methanesulfonate

ster of 3-benzyloxybenzyl alcohol, in 67% overall yield as a viscous liquid, after flash chromatography eluting with 30-100% EtOAc in hexane, IR (CHCl₃) 3434, 2933, 1681, 1500, 1401, 1256, 1054, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 1.77 (br s, 1H plus HDO), 2.20-2.34 (m, 2H), 3.91 (t, J = 5.5 Hz, 2H), 4.82 (dd, J = 7.5, 5.7 Hz, 1H), 5.02 (s, 2H), 5.11 (ABq, J_{AB} = 16.0 Hz, 2H), 6.85-7.01 (m, 7H), 7.22-7.41 (m, 6H); MH⁺ at m/z = 390; Anal. Calc'd for C₂₄H₂₃NO₄: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.61; H, 6.03; N, 3.55.

Reference Example 78

10

Intermediate 10508-84-A1

3,4-Dihydro-2-(2-hydroxyethyl)-4-(1-naphthylmethyl)-
3-oxo-2H-1,4-benzoxazine

Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
15 benzoxazine by Methods F and G, alkylating with 1-chloromethylnaphthalene, in 42% overall yield. the crude product was crystallized from ether/EtOAc/hexane to afford a white solid, mp 100-104°C; IR (KBr) 3435, 2896, 1668, 1504, 1414, 1253, 1132, 1068, 768, 758 cm⁻¹; ¹H NMR (CDCl₃) δ 1.92 (br s, 1H plus HDO), 2.26-2.44 (m, 2H), 3.96 (t, J = 5.6 Hz, 2H), 4.94 (dd, J = 7.5, 5.6 Hz, 1H), 5.62 (ABq, J_{AB} = 16.9 Hz, 2H), 6.72 (dd, J = 8.0, 1.1 Hz, 1H), 6.84 (td, J = 8.1, 1.5 Hz, 1H), 6.96-7.11 (m, 3H), 7.36 (t, J = 7.4 Hz, 1H), 7.54-7.64 (m, 2H), 7.78 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H); MH⁺ at m/z = 334; Anal. Calc'd for C₂₁H₁₉NO₃: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.56; H, 5.80; N, 4.14.

25

Reference Example 79

Intermediate 10508-80-1

3,4-Dihydro-2-(2-hydroxyethyl)-4-(2-naphthylmethyl)-
3-oxo-2H-1,4-benzoxazine

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Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
benzoxazine by Methods F and G, alkylating with 2-chloromethyl
naphthalene, in 81% overall yield. the crude product was crystallized from
ether/hexane to afford a white solid, mp 81-87°C; IR (KBr) 3459, 2940, 1665,
35 1500, 1403, 1277, 1242, 1066, 746 cm⁻¹; ¹H NMR (CDCl₃) δ 2.23-2.40 (m, 3H), 3.95 (t, J = 5.4 Hz, 2H), 4.90 (dd, J = 7.6, 5.6 Hz, 1H), 5.32 (ABq, J_{AB} = 16.1 Hz, 2H), 6.87-7.03 (m, 4H), 7.38 (d, J = 8.5 Hz, 1H), 7.43-7.48 (m, 2H).

7.67 (s, 1H), 7.75-7.84 (m, 3H); MH^+ at m/z = 334; Anal. Calc'd for $\text{C}_{21}\text{H}_{19}\text{NO}_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.65; H, 5.71; N, 4.02.

Reference Example 80

5

Intermediate 10508-79

4-(5-Chloro-2-thienylmethyl)-3,4-dihydro-2-(2-hydroxyethyl)-
3-oxo-2H-1,4-benzoxazine

- Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
10 benzoxazine by Methods F and G, alkylating with 5-chloro-2-(chloromethyl)thiophene and was isolated in 83% overall yield as a light
yellow viscous oil after flash chromatography using 30-50% EtOAc in
hexane; IR (CHCl_3) 3418, 2943, 1677, 1500, 1400, 1278, 1062, 750 cm^{-1} ;
 ^1H NMR (CDCl_3) δ 2.11-2.32 (m, 3H), 3.89 (q, J = 5.4 Hz, 2H), 4.78 (dd, J =
15 7.6, 5.5 Hz, 1H), 5.15 (ABq, J_{AB} = 16.0 Hz, 2H), 6.74 (d, J = 3.7 Hz, 1H), 6.84
(d, J = 3.7 Hz, 1H), 7.01-7.08 (m, 4H); MH^+ at m/z = 324; Anal. Calc'd for
 $\text{C}_{15}\text{H}_{14}\text{ClNO}_3\text{S} \cdot 0.25 \text{H}_2\text{O}$: C, 54.88; H, 4.45; N, 4.27; S, 9.77. Found: C,
54.86; H, 4.41; N, 4.04; S, 9.87.

20

Reference Example 81

Intermediate 11758-71-2

Methyl 4-[3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazin-
4-yl]methylbenzoate

- 25 Prepared from 2-(2-tert-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
benzoxazine by methods F and G, alkylating with 4-(methoxycarbonyl)-
benzyl chloride, to afford the alcohol as a white solid in 65% yield, mp=94-
95°C; ^1H NMR (CDCl_3) δ 8.00 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H),
6.95-7.04 (m, 2H), 6.89 (dt, J = 2.1, 8.0 Hz, 1H), 6.77 (dd, J = 7.8, 1.5 Hz, 1H),
30 5.20 (s, 2H), 4.86 (dd, J = 5.4, 7.7 Hz, 1H), 3.82-3.96 (m, 5H with 3H singlet
at δ 3.89), 2.16-2.37 (m, 3H, one of which is exchangeable). ^{13}C NMR
(CDCl_3) δ 166.8, 166.5, 144.1, 141.1, 130.1 (CH), 129.4, 128.4, 126.3 (CH),
124.2 (CH), 122.8 (CH), 117.3 (CH), 115.2 (CH), 75.1 (CH), 58.7 (CH₂), 52.0
(CH₃), 45.1 (CH₂), 33.1 (CH₂). IR 3450-3500 (br), 1719, 1660 cm^{-1} . MS
35 342 (MH^+), 324 (M-OH)⁺, 310 (M-OMe)⁺. Anal. Calc'd. for $\text{C}_{19}\text{H}_{19}\text{NO}_5$: C,
66.85; H, 5.61; N, 4.10. Found: C, 66.48; H, 5.47; N, 3.97.

Reference Example 82

Intermediate 11758-93-2A

Methyl 3-[3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazin-4-yl]methylbenzoate

5

Prepared from 2-(2-*tert*-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by methods F and G, alkylating with 3-(methoxycarbonyl)-benzyl chloride, and isolated as a white powder in 87% yield, mp 73-75°C; ¹H NMR (CDCl₃) δ 7.92-7.95 (m, 2H), 7.38-7.43 (m, 2H), 6.96-7.03 (m, 2H), 6.91 (dt, J = 2.3, 7.3 Hz, 1H), 6.81 (dd, J = 1.4, 7.7 Hz, 1H), 5.23 (d, J = 16.3 Hz, 1H), 5.16 (d, J = 16.3 Hz, 1H), 4.87 (dd, J = 5.7, 7.4 Hz, 1H), 3.92-3.95 (m, 2H), 3.91 (s, 3H), 2.21-2.37 (m, 3H containing one exchangeable hydrogen). ¹³C NMR (CDCl₃) δ 166.9, 166.7, 144.2, 136.5, 130.9 (CH), 130.7, 129.1 (CH), 128.7 (CH), 128.5, 127.7 (CH), 124.3 (CH), 122.9 (CH), 117.4 (CH), 115.4 (CH), 75.3 (CH), 58.9 (CH₂), 52.2 (CH₂), 45.1 (CH₂), 33.3 (CH₂). IR 3569, 2948, 1709, 1676, 1502 cm⁻¹. MS 342 (MH⁺). Anal. Calc'd. for C₁₉H₁₉NO₅: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.37; H, 5.62; N, 3.97.

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Reference Example 83

Intermediate 11758-82-2

Ethyl 2-[3,4-Dihydro-2-(2-hydroxyethyl)-3-oxo-2H-1,4-benzoxazin-4-yl]methylbenzoate

25

Prepared from 2-(2-*tert*-Butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine by methods F and G, alkylating with 2-(methoxycarbonyl)-benzyl chloride, and isolated as a white solid in 38% yield overall, mp 114-115.5°C (EtOAc/Hexanes). ¹H NMR (CDCl₃) δ 8.08 (dd, J = 1.4, 7.8 Hz, 1H), 7.40 (dt, J = 1.3, 7.5 Hz, 1H), 7.33 (br t, J = 7.6 Hz, 1H), 6.97-7.06 (m, 3H), 6.89 (dt, J = 1.9, 7.5 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.63 (d, J = 18.0 Hz, 1H), 5.54 (d, J = 18.0 Hz, 1H), 4.88 (dd, J = 5.7, 7.4 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.90-3.95 (m, 2H), 2.23-2.35 (m, 2H), 1.43 (t, J = 7.1 Hz, 3H). IR 3450-3550 (br), 1675, 1502 cm⁻¹. MS 356 (MH⁺). Anal. Calc'd. for C₂₀H₂₁NO₅: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.29; H, 5.97; N, 3.83.

35

Reference Example 84

Intermediate 11578-190

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-
2H-pyrido[4,3-b]-1,4-oxazine

5

Freshly prepared 4-hydroxypyridine nitrate was nitrated by the procedure of D. Rasala and R. Gawinecki, Org. Prep. Proc. Int., 1985, 17, 409-423. An EtOH solution of this nitropyridine (1 eq) and NaOAc (1 eq) was reduced with 10% Pd/C (10% w/w) under a hydrogen atmosphere at 50 psig for 4 h.

- 10 The crude 3-amino-4-hydroxypyridine was dissolved in DMF (5 mL) and treated with NaH (1.2 eq). This mixture was then treated with α -bromo- γ -butyrolactone (1.2 eq) at room temperature under nitrogen. After stirring at room temperature for 24 h, the DMF solution was treated with imidazole (1.2 eq) and *t*-butyldimethylsilyl chloride (1.2 eq). This solution was stirred for 16 h and then quenched with H₂O. The aqueous solution was extracted with EtOAc and the combined extract was washed with H₂O and dried over MgSO₄. The EtOAc solution was filtered through SiO₂ and concentrated under vacuum to afford the intermediate silyloxy compound in 14% yield. This material was alkylated by Method F, with 3-chlorobenzyl bromide, and
- 15 then deprotected with TFA (20% v/v) in CHCl₃ to afford the alcohol in 41% yield as a white crystalline solid; IR (KBr) 3519, 1664, 1393, 1320, 1192, 1082, 1054, 868 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.97-2.09 (m, 2H), 3.58-3.62 (m, 2H), 4.75 (t, J = 5.0, 1H), 5.10 (dd, J = 8.5, 4.2 Hz, 1H), 5.21 (s, 2H), 7.07 (d, J = 5.3 Hz, 1H), 7.25 (br d, J = 6.8 Hz, 1H), 7.35-7.43 (m, 3H), 8.13 (d, J = 5.8 Hz, 1H), 8.20 (s, 1H); MH⁺ at m/z = 319.
- 20
- 25

Reference Example 85

Intermediate 11721-108-1

3,4-dihydro-2-(2-hydroxyethyl)-[4-(3-thienylmethyl)]-
3-oxo-2H-1,4-benzoxazine

30

- Tributyl phosphine (1.5 eq) and 1,1'-(azodicarbonyl)dipiperidine (1.5 eq) were added to a solution of 2-(2-*tert*-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine (1 eq) in CH₂Cl₂ at room temperature. 3-thiophenemethanol (1.5 eq) was added dropwise and the mixture was stirred for 16 hours at room temperature. Hexane was added and this mixture was filtered and concentrated in vacuo. The oily residue was
- 35

purified by column chromatography using 1-2% EtOAc/CH₂Cl₂ as an eluent to give the alkylated intermediate as yellow oil; MH⁺ at m/z = 404.

The alkylated intermediate was treated following the procedure of method G to give the title compound as a clear oil. IR (n_D) 3427, 3101, 1681, 1500,

- 5 1060, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 2.1-2.4 (m, 2H), 3.8-4.0 (m, 2H), 4.15 (q, 1H), 4.80 (t, 1H), 5.21 (s, 2H), 7.07 (m, 5H), 7.1 (m, 1H), 7.25-7.3 (m, 1H); MH⁺ at m/z = 289.

Reference Example 86

10

Intermediate 11653-24A

4-(2-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-7-nitro-
2H-1,4-benzoxazine

Prepared from 2-(2-*tert*-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-

- 15 benzoxazine by methods F and G, alkylating with 2-chlorobenzyl bromide, to give a yellow solid: mp 106-108°C; MS (Cl) 363 (MH⁺); IR (KBr) 3268, 3122, 3088, 3068, 2969, 2937, 2881, 1888, 1794, 1571, 1478, 1210, 1148, 1135, 1116, 972, 926, 864, 705, 626, 475 cm⁻¹; ¹H NMR (CDCl₃/TMS) δ 7.90 (d, 1H, J=2.42Hz), 7.84 (dd, 1H, J=2.51, 8.91Hz), 7.45 (d, 1H, J=7.77Hz), 7.20 (m, 2H), 6.95 (d, 1H, J=7.52Hz), 6.81 (d, 1H, J=8.90Hz), 5.29 (s, 2H), 5.00 (dd, 1H, J=5.13, 7.90Hz), 3.95 (q, 2H, J=5.51Hz), 2.30 (brm, 2H), 1.86 (t, 1H, J=5.47); Anal. Calc'd for C₁₇H₁₅CIN₂O₅: C 56.29, H 4.17, N 7.72..
Found: C 56.25, H 4.24, N 7.60.

25

Reference Example 87

Intermediate 11653-35B

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-3-oxo-7-nitro-
2H-1,4-benzoxazine

- 30 Prepared from 2-(2-*tert*-butyldimethylsiloxyethyl)-3,4-dihydro-3-oxo-2H-1,4-
benzoxazine by methods F and G, alkylating with 3-chlorobenzyl bromide, to give a yellow solid: mp 100-102.5 °C; MS (Cl) 363 (MH⁺); IR (KBr) 3512, 3092, 3058, 2980, 2939, 2886, 1888, 1600, 1518, 1498, 1475, 1443, 1431, 1278, 1204, 1107, 1080, 1020, 863, 681, 602, 452 cm⁻¹; ¹H NMR (CDCl₃/TMS) δ 7.89(d, 1H, J=2.46Hz), 7.84(dd, 1H, J=2.53, 8.84Hz), 7.27(m, 3H), 7.10(m, 1H), 6.90(d, 1H, J=8.85Hz), 5.17(s, 2H), 4.99(dd, 1H, J=5.13, 7.85Hz), 3.94(m, 2H), 2.35(m, 1H), 2.24(m, 1H), 1.92(t, 1H,

J=5.40Hz); Anal. Calc'd for C₁₇H₁₅ClN₂O₅: C 56.29, H 4.17, N 7.72.. Found: C 56.25, H 4.09, N 7.63.

Reference Example 88

5

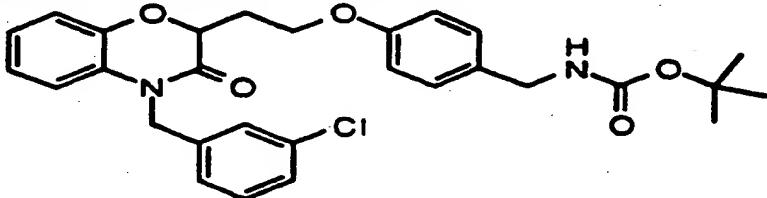
Intermediate 10840-117-1

3,4-Dihydro-2-(2-hydroxyethyl)-4-methyl-7-nitro-3-oxo-
2H-1,4-benzoxazine

Prepared from intermediate 11653-23 (Reference Example 31) by methods
10 F and G, alkylating with methyl iodide, to give an oil: Anal. Calc'd for
C₁₁H₁₃NO₃·9/10 H₂O: C 62.14, H 6.41, N 6.59.. Found: C 62.21, H 6.27, N
6.42

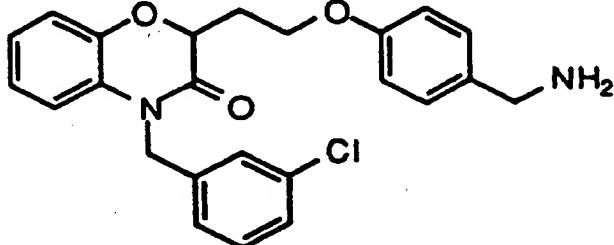
Compound 1

15 2-[2-[4-(1-Butoxycarbonylaminomethyl)phenoxy]ethyl]-
4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



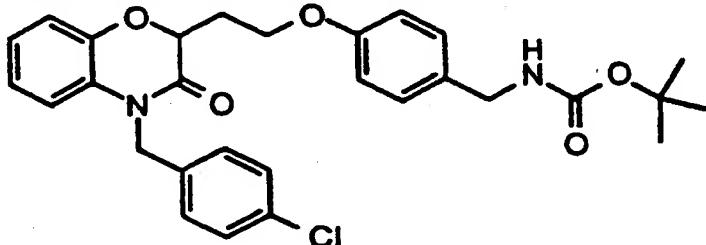
Method J: Intermediate 10488-22 (7.65 g, 1 eq, Reference Example 66), was dissolved in THF. Triphenylphosphine (0.5 g, 1.1 eq) and 4-(N-t-butoxycarbonyl)aminomethylphenol (0.38 g, 1 eq) were added, followed by dropwise addition of diethyl azodicarboxylate (0.303 ml, 1.1 eq). The reaction was stirred at reflux temperature for 48 h and concentrated under vacuum. The residue was triturated with Et₂O and the precipitate removed by filtration. The product was isolated from the filtrate by flash chromatography, eluting with EtOAc/hexanes. Fractions containing product
20 were crystallized from EtOAc/hexanes to afford a 50% yield of a white powder, mp 99-100°C; IR (KBr) 3386, 2981, 1692, 1613, 1501, 1393, 1366, 1248, 1171, 1053, 862, 752, 388 cm⁻¹; ¹H NMR (CDCl₃) δ 7.29-7.2 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.13 (m, 1H), 7.04-6.91 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.82 (dd, *J* = 8, 1.4 Hz), 5.17 (d, *J* = 16 Hz, 1H), 5.08 (d, *J* = 16 Hz, 1H).
25 4.94 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.75 (br s, 1H), 4.24 (m, 4H), 2.56 (m, 1H), 2.34 (m, 1H), 1.46 (s, 9H). Anal. Calc'd for C₂₉H₃₁ClN₂O₅: C 66.60, H 5.97, N 5.36. Found: C 66.41, H 6.00, N 5.34.

Compound 2
2-[2-[4-(Aminomethyl)phenoxy]ethyl]-
4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- 5 **Method K:** Compound 1 was dissolved in isopropyl alcohol containing an excess of HCl (g) (0.2-0.3 g/ml) and stirred at room temperature 2h. The product was filtered from the reaction mixture and the solid was washed with Et₂O to afford an 87% yield of a white solid, mp 194-200 (dec); MS (Cl) MH⁺ 422; IR (KBr) 2930, 1609, 1503, 1404, 1306, 1283, 1248, 1182, 1111, 1051, 833 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.45-8.24 (brs, 2H), 7.42 (d, 2H, *J* = 8.6Hz), 7.35 (m, 2H), 7.22 (d, 1H, *J* = 6.8Hz), 7.05 (m, 5H), 5.23 (d, 1H, *J* = 16.5Hz), 5.13 (d, 1H, *J* = 16.5Hz), 5.00 (dd, 1H, *J* = 4.2, 8.6Hz), 4.22 (m, 2H), 3.94 (br t, 2H, *J* = 2.5Hz), 3.39 (br s, 2H), 2.40 (m, 1H), 2.25 (m, 1H). Anal. Calc'd for C₂₄H₂₂ClN₂O₃ · HCl: C 62.89, H 5.06, N 6.11. Found: C 62.49, H 5.21, N 6.03.

Compound 3
2-[2-[4-(1-Butoxycarbonylaminomethyl)phenoxy]ethyl]-
4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



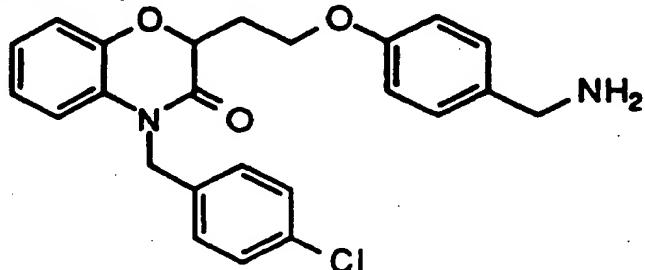
- 20 Prepared by method J, using intermediate 10353-28-1, (Reference Example 41) modified by stirring at room temperature for 48 h, in 54% yield as a white solid, mp 121-122.5°C; IR (KBr) 3400, 2977, 2931, 1690, 1613, 1516, 1503, 1468, 1436, 1395, 1366, 1301, 1277, 1248, 1171, 1094, 1053, 1014, 753 cm⁻¹; ¹H NMR (CDCl₃) δ 7.33-7.22 (m, 2H), 7.22-7.15 (m, 4H), 7.03-6.8 (m, 6H), 5.16 (d, *J* = 16.6 Hz, 1H), 5.08 (d, *J* = 16.6 Hz, 1H), 4.92 (dd, *J* = 9.4, 4.1Hz, 1H), 4.76 (br s, 1H), 4.25 (m, 4H), 2.57 (m, 1H), 2.33 (m, 1H), 1.47 (s, 1H).

9H). Anal. Calc'd for C₂₉H₃₁CIN₂O₅: C 66.60, H 5.97, N 5.36. Found: C 66.48, H 5.86, N 5.32.

Compound 4

5

2-[2-[4-(Aminomethyl)phenoxy]ethyl]-
4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

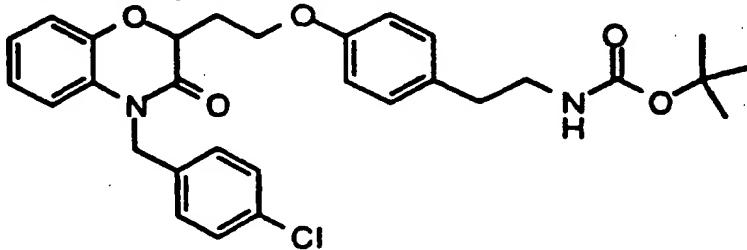


Prepared by method K using Compound 3. The HCl/isopropanol solution was evaporated under vacuum and the product isolated by crystallization from CH₂Cl₂/Et₂O in 76% yield as white solid, mp 200-201°C; IR (KBr) 3480, 3360, 3235, 2910, 2878, 1681, 1609, 1519, 1503, 1465, 1401, 1281, 1243, 1183, 1110, 1023, 913, 830, 797, 749, 569, 529 530 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.18 (br s, 3H), 7.40 (m, 4H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.02 (m, 6H), 5.21 (d, *J* = 16.8 Hz, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 4.98 (dd, *J* = 9.2, 4.4 Hz, 1H), 4.23 (m, 2H), 3.96 (m, 2H), 2.39 (m, 1H), 2.25 (m, 1H). Anal. Calc'd for C₂₄H₂₃CIN₂O₃ · HCl · 0.5 H₂O: C 61.54, H 5.38, N 5.98. Found: C 61.30, H 5.33, N 5.90.

Compound 5

20

2-[2-[4-(2-(t-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-
4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

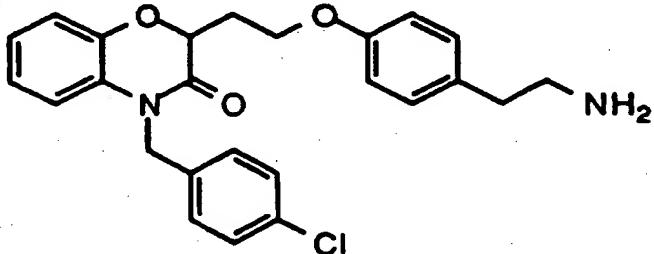


Method L: The alcohol intermediate 10353-28-1 (0.6 g, 1 eq Reference Example 41) was dissolved in dry benzene (6 ml) and treated with tributylphosphine (0.63 ml, 1.5eq) and boc-protected 4-(2-aminoethyl)phenol (0.66 g, 1.5 eq). The resulting solution was cooled in an ic bath and 1,1'-(azodicarbonyl)dipiperidine (ADDP, 0.71 g, 1.5 eq) was added in ne portion. The reaction was warm d to room temperature after

10 min. After 20 h, diluted with Et₂O and the white precipitate was filtered off. The filtrate was washed with 2N NaOH and concentrated. The product was isolated by flash chromatography eluting with acetone/hexanes. Recrystallization from EtOAc/hexanes afforded a 72% yield of the product as
 5 a white solid 108-109°C; MS (Cl) 537 (MH⁺); IR (KBr) 3378, 2979, 1798, 1609, 1515, 1500, 1395, 1368, 1246, 1171, 1061, 816, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 7.39 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.04-6.80 (m, 4H), 6.86 (d, J = 8.7 Hz, 2H), 5.14 (d, J = 16.4 Hz, 1H), 5.11 (d, J = 16.4 Hz, 1H), 4.93 (dd, J = 9.5, 4.1 Hz, 1H), 4.52 (br s, 1H), 4.23
 10 (m, 2H), 3.34 (m, 2H), 2.74 (apparent t, J = 7.1 Hz, 2H), 2.56 (m, 1H), 2.33 (m, 1H), 1.44 (s, 9H). Anal. Calc'd for C₃₀H₃₃CIN₂O₅: C 67.09, H 6.19, N 5.22. Found: C 66.88, H 6.07, N 5.22.

Compound 6

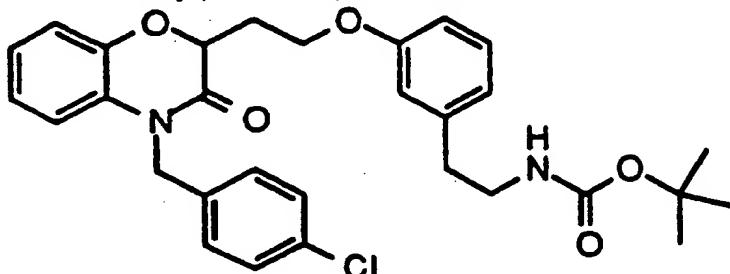
15 2-[2-[4-(2-Aminoethyl)phenoxy]ethyl]-
 4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by method K using Compound 5. The HCl/ isopropanol solution was evaporated under vacuum after 18 h and the product isolated by crystallization from CH₂Cl₂/Et₂O in 43% yield as white solid, mp 174-176°C; IR (KBr) 3415, 2933, 1681, 1609, 1503, 1465, 1401, 1279, 1241, 1065, 824, 789, 488, 428, 415 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.74 (br s, 3H), 7.39 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.1 (m, 4H), 6.93 (d, J = 8.8 Hz, 2H), 5.20 (d, J = 16.8 Hz, 1H), 5.13 (d, J = 16.8 Hz, 1H),
 20 4.97 (dd, J = 9.2, 4.1 Hz, 1H), 4.19 (m, 2H), 2.99 (m, 2H), 2.80 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H). Anal. Calc'd for C₂₅H₂₅CIN₂O₃ · HCl: C 63.43, H 5.54, N 5.92. Found: C 63.17, H 5.47, N 5.82.

Compound 7

2-[2-[3-(2-*t*-Butoxycarbonylaminoethyl)phenoxy]ethyl]-4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

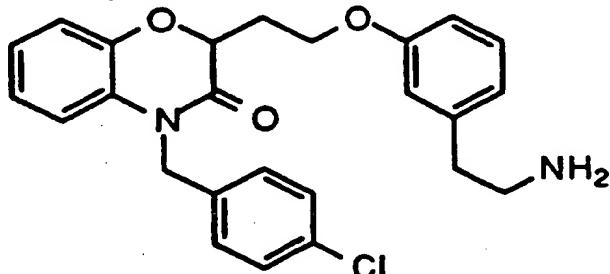


- 5 Prepared by method J using intermediate 10353-28-1 (Reference Example 41), modified by stirring at room temperature for 20 h, in 30% yield as a white solid; mp 97-98.5°C; IR (KBr) 3368, 3066, 3050, 2981, 2940, 1680, 1602, 1594, 1522, 1503, 1466, 1447, 1399, 1364, 1267, 1175, 1113, 1052, 1013 cm⁻¹; ¹H NMR (CDCl₃) δ 7.32-7.16 (m, 5H), 7.05-6.89 (m, 3H), 6.86-6.73 (m, 4H), 5.16 (d, *J* = 17.6 Hz), 5.09 (d, *J* = 17.6 Hz), 4.93 (dd, *J* = 6.7, 5.0 Hz), 4.55 (m, 1H), 4.23 (m, 2H), 3.38 (m, 2H), 2.78 (apparent t, *J* = 7.2 Hz, 2H), 2.58 (m, 1H), 2.33 (m, 1H), 1.43 (s, 9H). Anal. Calc'd for C₃₀H₃₃ClN₂O₅: C 67.09, H 6.19, N 5.22. Found: C 67.14, H 6.21, N 5.16.
- 10

15

Compound 8

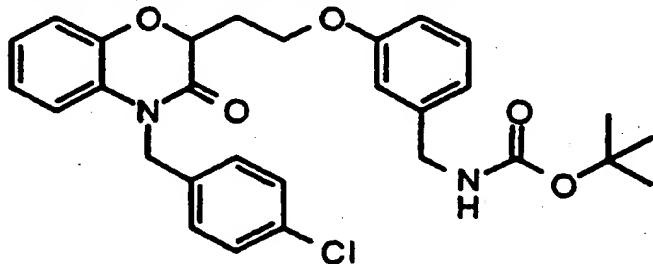
2-[2-[3-(2-Aminoethyl)phenoxy]ethyl]-4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- Prepared by method K using Compound 7. The HCl/isopropanol solution was evaporated under vacuum after 2.5h and the product isolated by crystallization from CH₂Cl₂/Et₂O in ~72% yield as a white solid, mp 155-156°C; IR (KBr) 3400, 3052, 2940, 1683, 1605, 1501, 1399, 1301, 1248, 1162, 1094, 1053, 751 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.35-7.23 (m, 3H), 7.02 (m, 4H), 6.86 (m, 3H), 5.2 (d, *J* = 17.0 Hz, 1H), 5.14 (d, *J* = 17 Hz, 1H), 5.15-3.30 (v br s, 4H), 4.22 (m, 2H), 3.05 (m, 2H), 2.83 (m, 2H), 2.40 (m, 1H), 2.25 (m, 1H). Calc'd for C₂₅H₂₅ClN₂O₃ · C₂H₂O₄ · 0.75 H₂O: C 60.00, H 5.32, N 5.18. Found: C 60.11, H 5.08, N 5.06.
- 20
- 25

Comp und 9

**2-[2-[3-(1-Butoxycarbonylaminomethyl)phenoxy]ethyl]-
4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine**



5

Prepared by method J, using intermediate 10353-28-1 (Reference Example 41) and modified by stirring at room temperature for 24 h, in 50% yield. Trituration with hot Et₂O afforded a white solid, mp 114-116°C; IR (KBr)

3365, 2985, 1686, 1600, 1526, 1503, 1451, 1395, 1366, 1268, 1173, 1129,

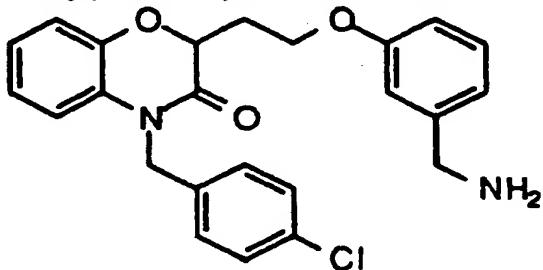
10 1067, 1052, 843, 787, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 7.29 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.9 Hz, 2H), 7.15-6.78 (m, 7H), 5.15 (d, J = 16.8 Hz, 1H), 5.1 (d, J = 16.8 Hz, 1H), 4.93 (dd, J = 9.2, 4.2 Hz, 1H), 4.82 (br s, 1H), 4.37-4.13 (m, 4H), 2.57 (m, 1H), 2.34 (m, 1H), 1.46 (s, 9H). Anal.

Calc'd for C₂₉H₃₁ClN₂O₅: C 66.60, H 5.97, N 5.36. Found: C 66.62, H 5.90,

15 N 5.33.

Compound 10

**2-[2-[3-(Aminomethyl)phenoxy]ethyl]-
4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine**



20

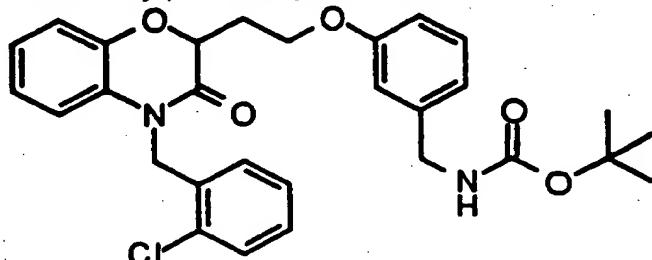
Prepared by method K, using Compound 9. The HCl/isopropanol solution was evaporated under vacuum after 24 h and the product isolated in 30% yield by conversion to the oxalate salt followed by trituration with hot CH₂Cl₂. mp 127-129°C; IR (KBr) 3446, 3053, 1501, 1466, 1401, 1248, 797,

25 747, 700, 486, 428 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.20 (br s, 1H), 7.40 (d, J = 8.4 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 5.21 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 17.2 Hz, 1H), 4.98 (dd, J = 9.2, 4.2, 1H), 5.15-4.10

(v br s, 3H), 4.22 (m, 2H), 4.01 (s, 2H), 2.45 (m, 1H), 2.27 (m, 1H). Calc'd for C₂₄H₂₃CIN₂O₃ · C₂H₂O₄ · 1.5 H₂O; C 57.83, H 5.23, N 5.19. Found: C 58.06, H 4.85, N 5.20.

5

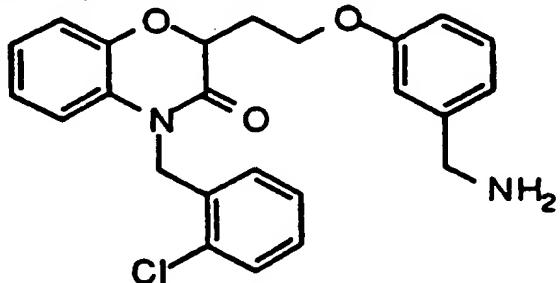
Compound 11
2-[2-[3-(1-Butoxycarbonylaminomethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by method J, using intermediate 9086-189-1 (Reference Example 42), without chromatography. The product was isolated by precipitation from aqueous methanol and made basic by dropwise addition of 2N NaOH, followed by recrystallization from MeOH/water, in 84% yield mp 115-116°C; MS (Cl) 523 (MH⁺); IR (KBr) 3357, 2979, 1686, 1611, 1586, 1526, 1505, 1466, 1449, 1395, 1368, 1285, 1252, 1165, 1052, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43 (dd, J = 7.6, 1.7 Hz, 1H), 7.27-7.13 (m, 4H), 7.16-6.96 (m, 3H), 6.95-6.81 (m, 3H), 6.73 (dd, J = 8.4, 1.3 Hz, 1H), 5.28 (d, J = 17.8 Hz, 1H), 5.21 (d, J = 17.8 Hz, 1H), 4.97 (dd, J = 9.4, 4.2 Hz, 1H), 4.82 (br s, 1H), 4.35-4.17 (m, 4H), 2.59 (m, 1H), 2.37 (m, 1H), 1.47 (s, 9H). Anal. Calc'd for C₂₉H₃₁CIN₂O₅: C 66.60, H 5.97, N 5.36. Found: C 66.59, H 5.87, N 5.30.

20

Compound 12
2-[2-[3-(Aminomethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



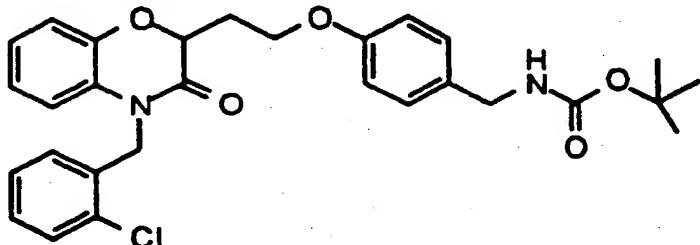
25 Prepared by method K, using Compound t1. The HCl/isopropanol solution was evaporated under vacuum after 20 h and the product isolated by crystallization from CH₂Cl₂ in 50% yield as a white powder; mp 191-193°C;

MS (Cl) 423 (MH⁺); IR (KBr) 3419, 2889, 2624, 1683, 1605, 1505, 1466, 1443, 1403, 1324, 1279, 1181, 1110, 1086, 1038, 951, 930, 893, 791, 749, 695, 627, 567, 452 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.35 (br s, 3H), 7.53 (dd, J = 7.7, 1.2 Hz, 1H), 7.32 (m, 3H), 7.17 (s, 1H), 7.13-6.95 (m, 6H), 6.85 (dd, J = 7.7, 1.2 Hz, 1H), 5.22 (d, J = 17.3 Hz, 1H), 5.13 (d, J = 17.3 Hz, 1H), 5.04 (dd, J = 8.8, 4.2 Hz, 1H), 4.25 (m, 2H), 4.0 (s, 2H), 2.44 (m, 1H), 2.30 (m, 1H). Anal. Calc'd for C₂₄H₂₃CIN₂O₃ · HCl · 0.5 H₂O: C 61.54, H 5.38, N 5.98. Found: C 61.35, H 5.08, N 5.87.

10

Compound 13

2-[2-[4-(*t*-Butoxycarbonylaminomethyl)phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

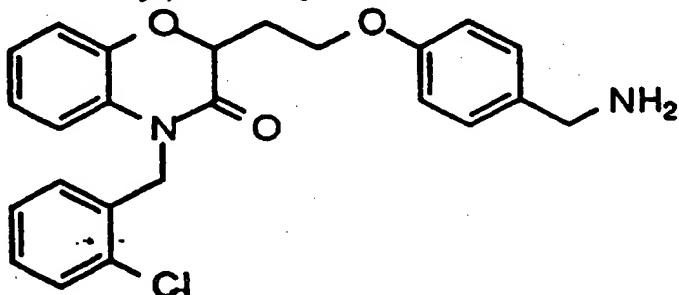


Prepared by method J using intermediate 9086-189-1 (Reference Example 42), in 50% yield as a white solid, mp 121-123°C; IR (KBr) 3345, 2979, 2925, 1683, 1611, 1503, 1466, 1401, 1248, 1171, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42 (dd, J = 7.8, 1.4 Hz, 1H), 7.27-7.12 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.05-6.87 (m, 4H), 6.88 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 7.8 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 17.6 Hz, 1H), 4.96 (dd, J = 9.4, 4.1 Hz, 1H), 4.76 (br s, 1H), 4.25 (m, 4H), 2.58 (m, 1H), 2.36 (m, 1H), 1.46 (s, 9H). Anal. Calc'd for C₂₉H₃₁CIN₂O₅: C 66.60, H 5.97, N 5.36. Found: C 66.35, H 5.82, N 5.72.

25

Compound 14

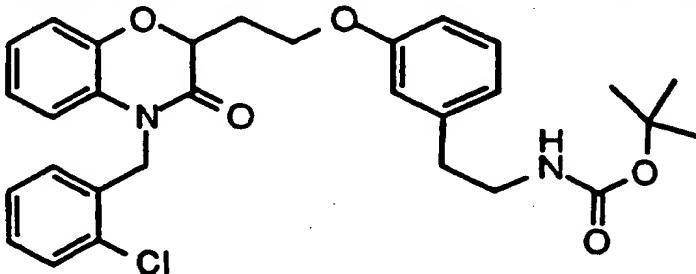
2-[2-[4-(Aminomethyl)phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by method K from Compound 13. The isopropanol was removed under vacuum and the product isolated by crystallization from CHCl₃/EtOAc in 69% yield as a white solid; mp 200-205°C; MS (CI) 423 (MH⁺); IR (KBr) 3430, 2960, 2890, 2600, 1690, 1611, 1517, 1501, 1468, 1401, 1279, 1250, 1183, 1050, 749, 407 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.22 (br s, 3H), 7.53 (dd, J = 7.6, 1.3 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.37-7.23 (m, 3H), 7.12-6.95 (m, 4H), 7.02 (d, J = 8.7 Hz, 2H), 6.83 (dd, J = 7.9, 1.6 Hz, 1H), 5.2 (d, J = 17.2 Hz, 1H), 5.13 (d, J = 17.2 Hz, 1H), 5.04 (dd, 8.4, 4.2 Hz, 1H), 4.25 (m, 2H), 3.95 (s, 2H), 2.42 (m, 1H), 2.39 (m, 1H). Anal. Calc'd for C₂₄H₂₃CIN₂O₃ · HCl · 0.3 H₂O: C 62.02, H 5.34, N 6.03. Found: C 61.99, H 5.20, N 5.87.

Compound 15

2-[2-[3-(2-(1-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

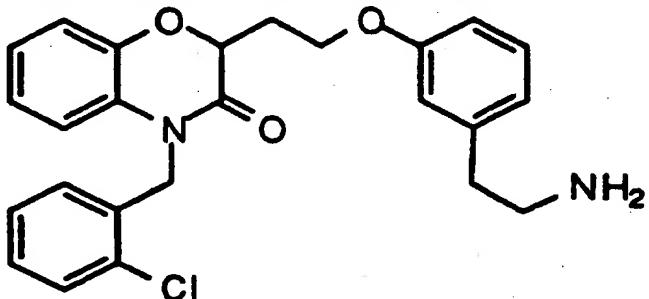


15

Prepared by method J using intermediate 9086-189-1 (Reference Example 42), in 48% yield as a white powder, mp 61-65°C (softens) 68-70°C; MS (CI) 537 (MH⁺); IR (KBr) 3365, 2998, 2935, 1690, 1607, 1503, 1447, 1401, 1366, 1254, 1171, 1050, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42 (dd, J = 7.6, 1.2 Hz, 1H), 7.35-7.13 (m, 3H), 7.08-6.87 (m, 4H), 6.85-6.68 (m, 4H), 5.28 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 1H), 4.97 (dd, J = 9.2, 4.1 Hz, 1H), 4.54 (br s, 1H), 4.25 (m, 2H), 3.37 (m, 2H), 2.66 (m, 2H), 2.59 (m, 1H), 2.38 (m, 1H), 1.44 (s, 9H). Anal. Calc'd for C₃₀H₃₃CIN₂O₅: C 67.09, H 6.19, N 5.22. Found: C 67.08, H 6.15, N 5.17.

25

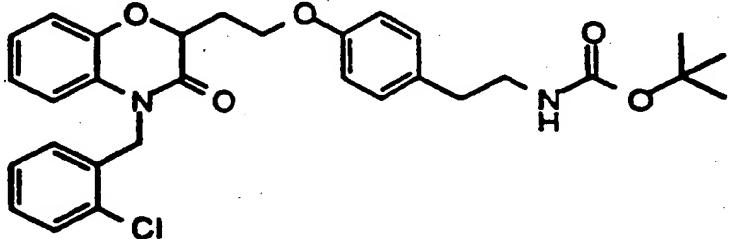
Compound 16
2-[2-[3-(2-Aminoethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- 5 Prepared by method K using Compound 15. The isopropanol was removed under vacuum after 3 h and the product isolated by crystallization from CHCl₃/EtOAc in 91% yield to afford a white solid, mp 173-175°C; MS (Cl) 437 (MH⁺); IR (KBr) 3420, 2932, 1687, 1603, 1501, 1466, 1445, 1401, 1326, 1252, 1160, 1050, 748, 695 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.94 (br s, 3H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.37-7.23 (m, 3H), 7.15-6.95 (m, 5H), 6.86 (m, 3H), 5.22 (d, *J* = 17.5 Hz, 1H), 5.13 (d, *J* = 17.5 Hz, 1H), 5.04 (dd, *J* = 9.2, 2.2 Hz, 1H), 4.23 (m, 2H), 3.04 (m, 2H), 2.35 (m, 2H), 2.4 (m, 1H), 2.29 (m, 1H). Anal. Calc'd for C₂₅H₂₅CIN₂O₃ · HCl · 0.2 H₂O: C 62.95, H 5.58, N 5.87. Found: C 62.83, H 5.29, N 5.62.
- 10

15

Compound 17
2-[2-[4-(2-(*t*-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

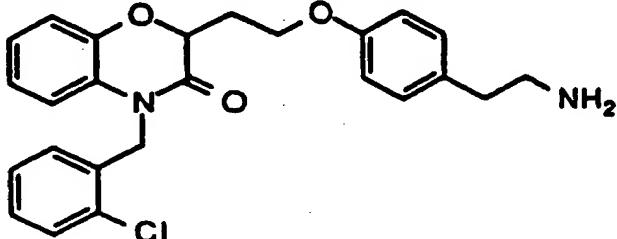


- 20 Prepared by method J using intermediate 9086-189-1 (Reference Example 42) in 33% yield as a white powder, mp 108-111°C; IR (KBr) 3378, 2978, 2920, 1692, 1611, 1515, 1503, 1397, 1366, 1248, 1175, 1056, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.26-7.13 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.06-6.88 (m, 4H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.28 (d, *J* = 17.8 Hz, 1H), 5.22 (d, *J* = 17.9 Hz, 1H), 4.97 (dd, *J* = 9.7, 4.2 Hz, 1H), 4.52 br s, 1H), 4.25 (m, 2H), 3.35 (m, 2H), 2.74 (apparent t, *J* = 7.1
- 25

Hz, 2H), 2.05 (m, 1H), 2.36 (m, 1H), 1.44 (s, 9H). Anal. Calc'd for C₃₀H₃₃CIN₂O₅: C 67.09, H 6.19, N 5.22. Found: C 66.71, H 6.00, N 5.58.

Compound 18

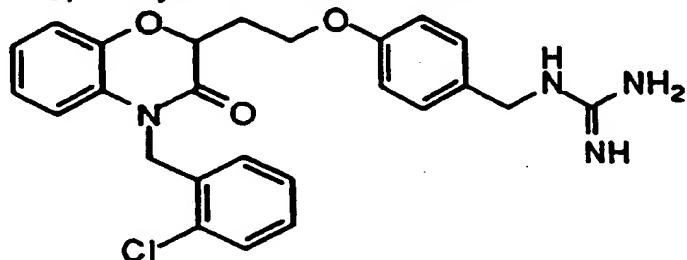
5 2-[2-[4-(2-Aminoethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by method K using Compound 18. The isopropanol was removed under vacuum after 1 h and the product isolated, by trituration with Et₂O, in 10 49% yield as an off white powder mp 143-148°C; MS (Cl) 437 (MH⁺ - H₂O); IR (KBr) 3365, 2930, 1686, 1609, 1515, 1503, 1468, 1445, 1401, 1252, 1111, 1050, 826, 747 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.97 (br s, 3H), 7.54 (dd, J = 7.7, 1.4 Hz, 1H), 7.37-7.22 (m, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.12-6.95 (m, 4H), 6.94 (d, J = 8.6 Hz, 2H), 6.83 (dd, J = 7.6, 1.5 Hz, 1H), 5.20 (d, J = 17.3 Hz, 1H), 5.13 (d, J = 17.3 Hz, 1H), 5.04 (dd, J = 9.1, 4.0 Hz, 1H), 4.21 (m, 2H), 2.99 (m, 2H), 2.82 (m, 2H), 2.40 (m, 1H), 2.27 (m, 1H). Anal. Calc'd for C₂₅H₂₅CIN₂O₃ · HCl · 0.5H₂O: C 62.24, H 5.64, N 5.81. Found: C 62.17, H 5.31, N 6.13.

Compound 19

20 4-(2-Chlorobenzyl)-2-[2-[4-(guanidinomethyl)phenoxy]ethyl]-
3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by method L using intermediate 9086-189-1 (Reference Example 42) and N,N'-di-t-butoxycarbonyl-(4-hydroxyphenyl)methylguanidine and 25 method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by dissolving the crude product or residue in aqueous methanol and treating with a dropwise addition of 2N NaOH until

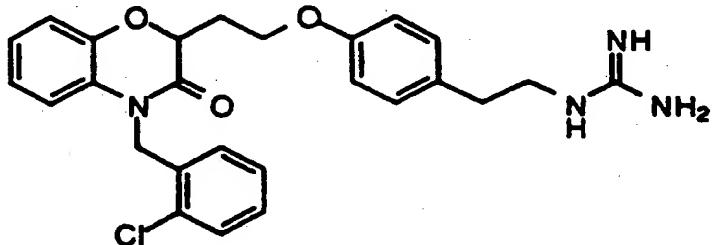
basic. The product oiled out of solution and removal of solvent by decantation afforded a viscous oil which was dried under vacuum and used without further purification. The deprotection step afforded the product, after crystallization in CH_2Cl_2 , in 71% overall yield as a white powder, mp 180-

- 5 182°C; MS (Cl) 465 (MH^+); IR (KBr) 3320, 3162, 1685, 1665, 1611, 1515, 1503, 1468, 1447, 1401, 1333, 1302, 1281, 1243, 1181, 1113, 1048, 824, 749, 687, 565, 428, 401 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 8.07 (br t, $J = 5.9$ Hz, 1H), 7.53 (dd, $J = 8.0$ Hz, 1H), 7.8-6.7 (v br s, 4H), 7.35-7.15 (m, 3H), 7.26 (d, $J = 9.0$ Hz, 2H), 7.1-6.93 (m, 3H), 6.99 (d, $J = 9.0$ Hz, 2H), 5.22 (d, $J = 17.9$ Hz, 1H), 5.11 (d, $J = 17.9$ Hz, 1H), 5.04 (dd, $J = 8.8, 4.2$ Hz, 1H), 4.3 (apparent d, $J = 6$ Hz, 2H), 4.23 (m, 2H), 2.41 (m, 1H), 2.28 (m, 1H). Anal. Calc'd for $\text{C}_{25}\text{H}_{25}\text{ClN}_4\text{O}_3 \cdot \text{HCl}$: C 59.89, H 5.23, N 11.17. Found: C 59.57, H 5.13, N 10.99.
- 10

15

Compound 20

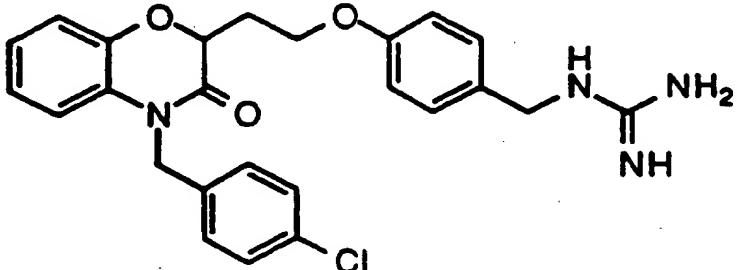
4-(2-Chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- 20 Prepared by method L using intermediate 9086-189-1 (Reference Example 42) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated, after flash chromatography and crystallization, in 36% yield. The deprotected product was isolated as the carbonate salt (tan solid) in 88% yield; mp 90°C (dec); MS (Cl) 479 (MH^+); IR (KBr) 3600, 3350, 2939, 1688, 1515, 1501, 1401, 1243, 1111, 1050, 834, 749, 522 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 7.53 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.33 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.29 (m, 1H), 7.25 (dd, 7.4, 1.6 Hz, 1H), 7.18 (d, $J = 8.2$ Hz, 2H), 7.12-6.93 (m, 4H), 6.9 (d, $J = 8.2$ Hz, 2H), 6.82 (dd, $J = 7.4, 1.6$ Hz, 1H), 5.21 (d, $J = 17.2$ Hz, 1H), 5.11 (d, $J = 17.2$ Hz, 1H), 5.2 (dd, $J = 8.5, 4.1$ Hz, 1H), 4.2 (m, 2H), 3.7-2.8 (br s, 5H), 2.69 (m, 2H), 2.4 (m, 1H), 2.25 (m, 1H). Anal. Calc'd for $\text{C}_{26}\text{H}_{27}\text{N}_4\text{O}_3\text{Cl} \cdot \text{H}_2\text{CO}_3 \cdot 0.3 \text{ H}_2\text{O}$: C 59.35, H 5.46, N 10.25, Cl 6.49. Found: C 59.37, H 5.29, N 10.25, Cl 6.86.
- 25
- 30

Compound 21

4-(4-Chlorobenzyl)-2-[2-[4-(guanidinomethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



5

Prepared by method L using intermediate 10353-28-1 (Reference Example 41) and N,N'-di-t-butoxycarbonyl-(4-hydroxyphenyl)methyl guanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by dissolving the crude product residue in aqueous methanol and treating with a dropwise addition of 2N NaOH until basic. The product precipitated out of solution and was collected by filtration. The resulting white solid was air dried and used without further purification. The deprotected product was isolated as the carbonate salt (tan solid) in 24% overall yield as a tan solid, mp 90°C (dec); MS (Cl) 465 (MH⁺); IR (KBr)

15

3330, 2940, 1685, 708, 1650, 1600, 1513, 1501, 1466, 1399, 1302, 1279, 1245, 1177, 1094, 1052, 799, 751 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.5-3.0 (v br s, 5H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.1-6.95 (m, 4H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 4.97 (dd, *J* = 9.0, 4.2 Hz, 1H), 4.28 (m, 2H), 2.37 (m, 1H),

20

2.23 (m, 1H). Anal. Calc'd for C₂₅H₂₅ClN₄O₃ · CH₂O₃ · 0.3 H₂O: C 58.66, H 5.23, N 10.52. Found: C 58.38, H 4.86, N 10.61.

Reference Example 89

Intermediate 10353-76

25

4-(2-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-2H-1,4-benzoxazine

Method M: Intermediate 9086-189-1 (1g, 1eq, Reference Example 42) was dissolved in THF (5 ml) and treated with 1M Borane/THF (6.3 ml, 3 eq), and heated to reflux. After 3h, the reaction mixture was concentrated under vacuum and the residue was partitioned between Et₂O and 1N HCl. The organic layer was washed with saturated Na₂CO₃, brine, dried over Na₂SO₄ and concentrated under vacuum. The product was isolated by flash

chromatography, eluting with EtOAc/hexanes, to afford a 96% yield of a colorless oil.

Reference Example 90

5

Intermediate 10353-82

4-(3-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-2H-1,4-benzoxazine

Prepared by Method M, from intermediate 10488-22 (Reference Example 66), and isolated in 99% yield.

10

Reference Example 91

Intermediate 10353-83

4-(4-Chlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-2H-1,4-benzoxazine

15 Prepared by Method M from intermediate 10353-28-1 (Reference Example 41) and isolated in quantitative yield as a colorless oil.

Reference Example 92

Intermediate 10840-45

20 3,4-Dihydro-2-(2-hydroxyethyl)-4-(4-methylbenzyl)-2H-1,4-benzoxazine

Prepared by Method M from intermediate 10840-33 (Reference Example 46) in 80% yield and isolated as a green oil, IR (neat) 3371, 2921, 1607, 1500, 1247, 1221, 1052, 743 cm⁻¹; ¹H NMR (CDCl₃) δ 1.77-2.00 (m, 3H), 2.33 (s, 3H), 3.19 (dd, J = 11.8, 7.7 Hz, 1H), 3.27 (dd, J = 11.7, 2.6 Hz, 1H), 3.86-3.94 (m, 2H), 4.33-4.40 (m, 1H), 4.40 (s, 2H), 6.60-6.71 (m, 2H), 6.76-6.84 (m, 2H), 7.15 (br q, J_{AB} = 8.2 Hz, 4H); Anal. Calc'd for C₁₈H₂₁NO₂·0.6H₂O: C, 73.49; H, 7.61; N, 4.76. Found: C, 73.33; H, 7.22; N, 4.84.

30

Reference Example 93

Intermediate 10840-46

3,4-Dihydro-2-(2-hydroxyethyl)-4-(3-methoxybenzyl)-
2H-1,4-benzoxazine

35 Prepared by Method M from 10508-22-A (Reference Example 76) in quantitative yield and isolated as a green oil, IR 3350, 2948, 1605, 1505, 1283, 1262, 1050, 743 cm⁻¹; ¹H NMR (CDCl₃) δ 1.50-2.10 (v br s, 1H), 1.78-2.01 (m, 2H), 3.20 (dd, J = 11.7, 7.8 Hz, 1H), 3.28 (dd, J = 11.7, 2.6 Hz, 1H),

3.78 (s, 3H), 3.88 (t, $J = 5.6$ Hz, 2H), 4.34-4.43 (m, 1H), 4.40 (s, 2H), 6.62-6.79 (m, 2H), 6.76-6.89 (m, 5H), 7.24 (t, $J = 7.7$ Hz, 1H); MH^+ at m/z = 300; Anal. Calc'd for $\text{C}_{18}\text{H}_{21}\text{NO}_3 \cdot 0.2\text{H}_2\text{O}$; C, 71.36; H, 7.12; N, 4.62. Found: C, 71.25; H, 7.00; N, 4.62.

5

Reference Example 94

Intermediate 10840-8

4-(2,4-Dichlorobenzyl)-3,4-dihydro-2-(2-hydroxyethyl)-
2H-1,4-benzoxazine

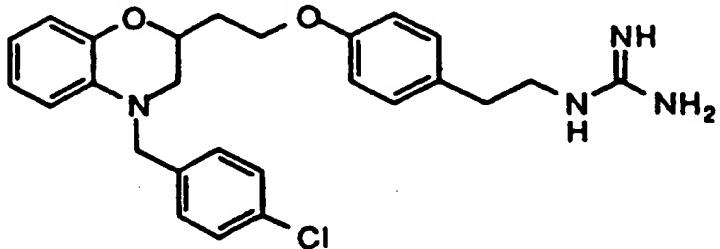
10

Prepared by Method M from 10005-181-1 (Reference Example 48) in 87% yield and was isolated as a colorless oil. IR (neat) 3348, 1607, 1501, 1247, 1221, 1046, 743 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.80-2.03 (m, 3H), 3.27-3.37 (m, 2H), 3.85-3.98 (m, 2H), 4.38-4.45 (m, 1H), 4.45 (s, 2H), 6.44 (dd, $J = 8.0$, 1.4 Hz, 1H), 6.65 (td, $J = 7.6$, 1.5 Hz, 1H), 6.77 (td, $J = 7.8$, 1.6 Hz, 1H), 6.83 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.15-7.25 (m, 2H), 7.42 (d, $J = 1.8$ Hz); MH^+ at m/z = 338; Anal. Calc'd for $\text{C}_{17}\text{H}_{17}\text{Cl}_2\text{NO}_2$; C, 60.37; H, 5.07; N, 4.14. Found: C, 60.04; H, 4.98; N, 4.05.

15

Compound 22

4-(4-Chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-
3,4-dihydro-2H-1,4-benzoxazine

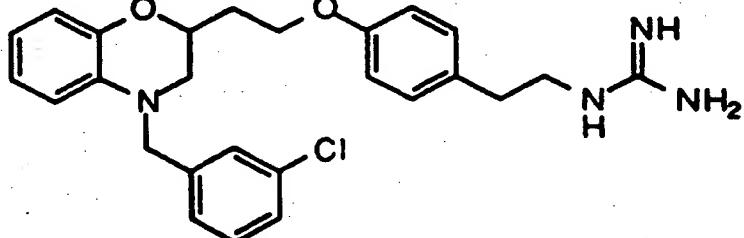


Prepared by method L using intermediate 10353-83 (Reference Example 91) and N,N'-di- t -butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated with satisfactory purity by flash chromatography (eluting with EtOAc/hexanes) in 58% yield. The deprotected product was isolated as the carbonate salt in 50% yield as a tan solid, single homogeneous peak by HPLC (PDA detection) 15cm C18 column, eluting with 55/45 H_2O (5% NH_4OH , 5% HOAC)/ CH_3CN ; MS (Cl) 466 (MH^+); IR (KBr) 3475, 3321, 3064, 2931, 2875, 1698, 1638, 1608, 1581, 1513, 1502, 1467, 1696, 1358, 1303, 1288, 1244, 1178, 1116, 1047, 1013, 833, 743 cm^{-1} .

1; ¹H NMR (DMSO-d₆) δ 8.30-7.50 (br s, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.2 Hz, 2H), 6.77-6.60 (m, 3H), 6.55 (m, 1H), 4.53 (d, J = 16.8 Hz, 1H), 4.45 (d, J = 16.8 Hz, 1H), 4.35 (m, 1H), 4.12 (br d, J = 11.4 Hz, 2H), 3.60-3.10 (br s, 5H), 3.49 (m, 5 H), 2.73 (m, 2H), 2.05 (m, 2H).

Compound 23

**4-(3-Chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-
3,4-dihydro-2H-1,4-benzoxazine**



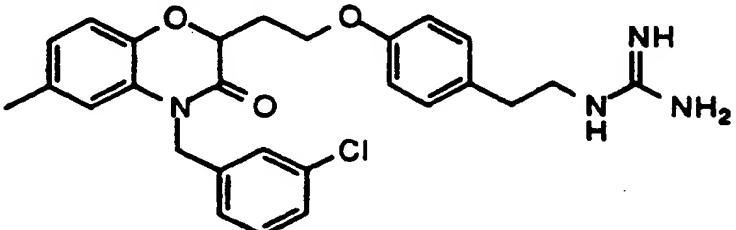
10 Prepared by method L using intermediate 10353-82 (Reference Example 90) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by flash chromatography (eluting with EtOAc/hexanes) in 94% yield. The deprotected product was isolated as the carbonate salt in 59% yield as a tan solid, single homogeneous peak by HPLC (PDA detection) 15cm C₁₈ column, eluting with 55/45 H₂O (5% NH₄OH, 5% HOAC)/CH₃CN; MS (Cl) 466 (MH⁺); IR (KBr) 3473, 3316, 3064, 2931, 2876, 1698, 1638, 1608, 1580, 1512, 1503, 1468, 1431, 1393, 1359,

15 1303, 1243, 1221, 1178, 833, 742 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.50-7.60 (br s, 2H), 7.42-7.20 (m, 4H), 7.19 (d, J = 7.7 Hz, 2H), 6.90 (d, J = 7.7 Hz, 2H), 6.78-6.70 (m, 3H), 6.58 (m, 1H), 4.55 (d, J = 17.3 Hz, 1H), 4.48 (d, J = 17.3 Hz, 1H), 4.15 (m, 2H), 3.80-3.10 (br s, 4H), 3.52 (br d, J = 11.8 Hz, 2H), 3.25 (m, 2H), 2.73 (m, 2H), 2.08 (m, 2H).

20 25

Compound 24

4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-6-methyl-3-oxo-2H-1,4-benzoxazine

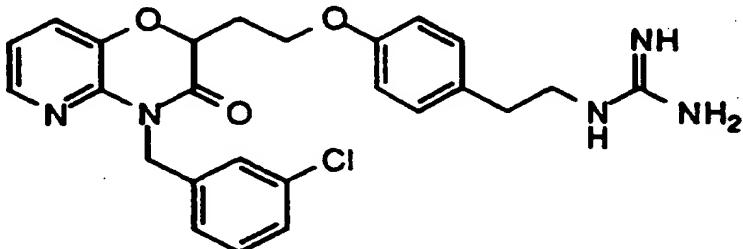


- 5 Prepared by method L using intermediate 12168-10-1 (Reference Example 39) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by flash chromatography (eluting with EtOAc/hexanes) in ~70% yield. The deprotected product was triturated from
- 10 Et₂O dissolved in CH₂Cl₂ and the solvent removed under vacuum to afford the product in 92% yield as a pale yellow solid, MS (Cl) 493 (MH⁺); IR (KBr) 3148, 1666, 1610, 1511, 1433, 1384, 1302, 1244, 1178, 1112, 1052, 817, 772, 680, 527 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.50 (br t, *J* = 5.7 Hz, 1H), 7.40-6.85 (v br s, 5H), 7.35 (m, 3H), 7.20 (m, 3H), 6.94 (m, 4H), 6.81 (d, *J* = 8.9 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 4.94 (dd, *J* = 9.1, 4.3 Hz, 1H), 4.18 (m, 2H), 3.31 (m, 2H), 2.72 (apparent t, *J* = 7.3 Hz, 2H), 2.37 (m, 1H), 2.30-2.13 (m, 1H), 2.19 (s, 3H). Anal. Calcd for C₂₇H₂₉CIN₄O₃ · HCl · 1.0 H₂O: C 59.23, H 5.89, N 10.23. Found: C 59.47, H 5.60, N 10.11.

20

Compound 25

4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-pyrido[3,2-b]-1,4-oxazine



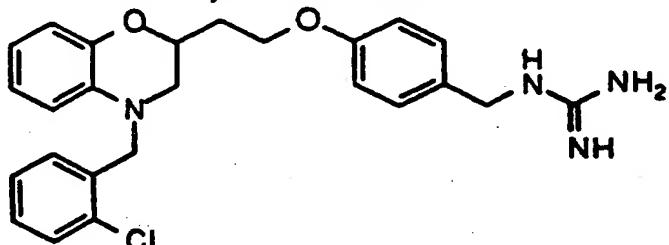
- Prepared by method L using intermediate 10353-191-1 (Reference Example 40) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by flash chromatography (eluting with EtOAc/hexanes) in 77% yield. The deprotected product was isolated in 50%

yield after trituration with Et₂O, mp 47-54°C (softens) 54-56°C; MS (Cl) 480 (MH⁺); IR (KBr) 3326, 3150, 1666, 1599, 1513, 1459, 1398, 1331, 1278, 1229 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.0 (dd, J = 4.9, 1.4 Hz, 1H), 7.53 (br t, J = 7.3 Hz, 1H), 7.47 (dd, J = 7.9, 1.2 Hz, 1H), 7.37 (s, 1H), 7.35-7.22 (m, 2H), 5 7.17 (d, J = 8.6 Hz, 2H), 7.09 (dd, J = 7.9, 4.8 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 5.24 (d, J = 16.3, Hz, 1H), 5.23 (d, J = 16.3 Hz, 1H), 5.12 (dd, J = 8.2, 4.2 Hz, 1H), 4.15 (m, 2H), 6.32 (m, 2H), 2.71 (m, 2H), 2.39 (m, 1H), 2.29 (m, 1H). Anal. Calc'd for C₂₅H₂₆CIN₅O₃ · 2HCl · 0.8 H₂O: C 56.57, H 5.43, N 13.19. Found: C 56.84, H 5.65, N 13.04.

10

Compound 25

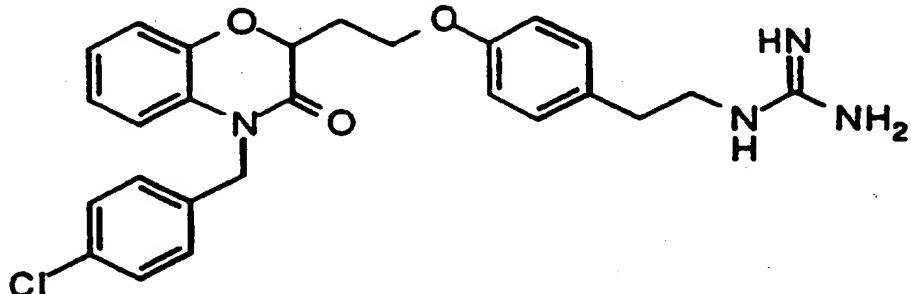
4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-6-methyl-2H-1,4-benzoxazine



15 Prepared by method L using intermediate 10353-191-1 (Reference Example 40) and N,N'-di-1-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by dissolving the crude product residue in aqueous methanol and treating with a dropwise addition of 2N NaOH until basic. The precipitate was collected by filtration. The resulting product was dissolved in ether, washed sequentially with 1N HCl, sat'd NaHCO₃, and brine, dried over Na₂SO₄ and concentrated under vacuum and used without further purification. The deprotected product was isolated as the carbonate salt in 22% yield as a tan solid, single homogeneous peak by HPLC (PDA detection) 15cm C18 column, eluting with 55/45 H₂O (5% NH₄OH, 5% HOAC)/CH₃CN; MS (Cl) 451 (MH⁺); IR (KBr) 3314, 3036, 2923, 1682, 1608, 1581, 1511, 14658, 1443, 1392, 1352, 1302, 1244, 1223, 1175, 1046, 742 cm⁻¹.
20
25

Compound 26

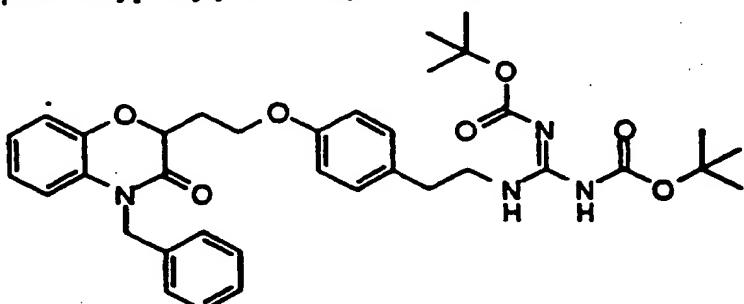
-4-(4-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-1,4-benzoxazine



- 5 Prepared by method L using intermediate 10353-28-1 (Reference Example 41) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by dissolving the crude product residue in aqueous methanol and treating with 2N NaOH until basic. The product 10 precipitated out of solution as a gummy semi-solid. The solvent was removed by decantation, the product was air dried and used without further purification. The deprotected product was isolated as the carbonate salt (tan solid) in 60% yield as a tan solid, single homogeneous peak by HPLC (PDA detection) 15cm C₁₈ column, eluting with 55/45 H₂O (5% NH₄OH, 5% HOAC)/CH₃CN; MS (Cl) 479 (MH⁺); IR (KBr) 3337, 3050, 2930, 2875, 1683, 1609, 1512, 1500, 1466, 1439, 1397, 1327, 1301, 1278, 1242, 1177, 1093, 750 cm⁻¹.

Compound 27

- 20 **4-Benzyl-2-{2-[4-[2-(*N,N*-bis-*tert*-butoxycarbonylguanidinoethyl]phenoxy}ethyl}-3,4-dihydro-3-oxo-2H-1,4-benzoxazine**



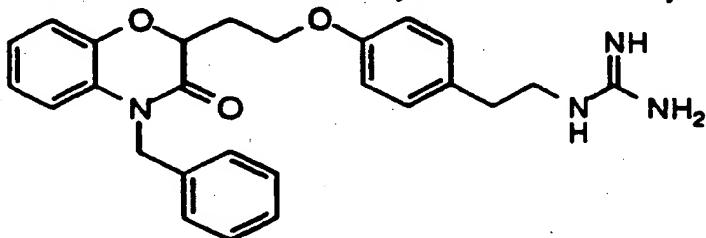
- Prepared by Method L using intermediate 10508-23-A (Reference Compound 74) and isolated as a white powder in 28% yield after column chromatography (10% ether in hexane); IR (KBr) 3334, 2978, 1638, 1616, 1330, 1132, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.25-2.39

(m, 1H), 2.50-2.63 (m, 1H), 2.81 (t, $J = 7.2$ Hz, 2H), 3.63 (q, $J = 7.9$ Hz, 2H), 4.18-4.29 (m, 2H), 4.94 (dd, $J = 9.3, 3.8$ Hz, 1H), 5.16 (s, 2H), 6.84-7.01 (m, 6H), 7.13 (d, $J = 8.4$ Hz, 2H), 7.23-7.34 (m, 5H), 8.38 (br t, $J = 3.8$ Hz, 1H), 11.49 (br s, 1H). Anal. Calc'd for C₃₆H₄₄N₄O₇: C, 67.06; H, 6.88; N, 8.69.

5 Found: C, 66.80; H, 6.90; N, 8.63.

Compound 28

4-Benzyl-3,4-dihydro-2-{2-[4-[2-guanidinoethyl]phenoxy]ethyl}-3-oxo-2H-1,4-benzoxazine Hydrochloride 0.7 Hydrate



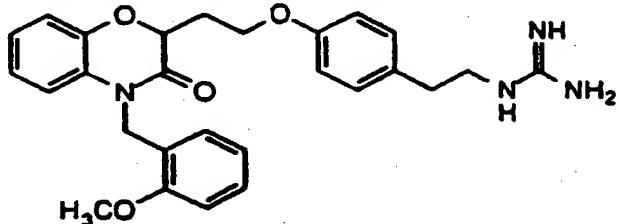
10

Prepared by Method K from Compound 27 and isolated as a white powder in 9.1% yield; IR (KBr) 3326, 3146, 1664, 1500, 1401, 1243, 827, 751 cm⁻¹; Anal. Calc'd for C₂₆H₂₈N₄O₃ · HCl · 0.7H₂O: C, 63.27; H, 6.21; N, 11.35. Found: C, 63.37; H, 5.98; N, 11.06.

15

Compound 29

3,4-Dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-4-(2-methoxybenzyl)-3-oxo-2H-1,4-benzoxazine



20

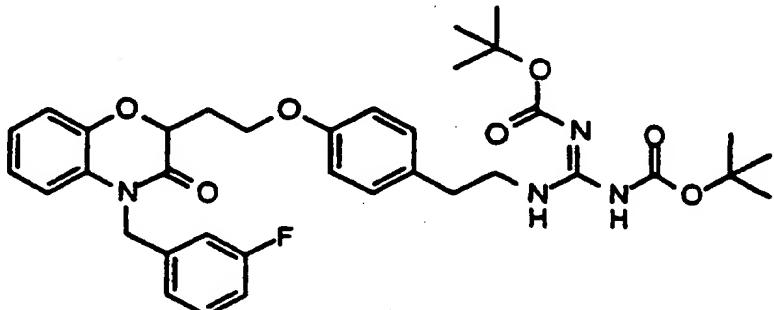
Prepared from 2-{2-[4-[2-(N,N-bis-tert-butoxycarbonylguanidino)ethyl]phenoxy]ethyl}-3,4-dihydro-4-(2-methoxybenzyl)-3-oxo-2H-1,4-benzoxazine by methods L and K to give an off-white powder in 25% yield; IR (KBr) 3164, 1663, 1501, 1405, 1245, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 2.20-2.33 (m, 1H), 2.37-2.52 (m, 1H), 2.76 (br s, 2H), 3.33 (br s, 2H), 3.87 (s, 3H), 4.08-4.21 (m, 2H), 4.87 (dd, $J = 8.6, 4.3$ Hz, 1H), 5.09 (ABq, $J_{AB} = 18.0$ Hz, 2H), 6.73-7.25 (v br s, 4H), 6.73-6.99 (m, 9H), 7.11 (d, $J = 7.7$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.67 (br s, 1H); MH⁺ at m/z = 475; Anal. Calc'd for C₂₇H₃₀N₄O₄ · HCl · 0.75H₂O: C, 61.83; H, 6.25; N, 10.68. Found: C, 61.82; H, 6.26; N, 10.61.

25

2.76 (br s, 2H), 3.33 (br s, 2H), 3.87 (s, 3H), 4.08-4.21 (m, 2H), 4.87 (dd, $J = 8.6, 4.3$ Hz, 1H), 5.09 (ABq, $J_{AB} = 18.0$ Hz, 2H), 6.73-7.25 (v br s, 4H), 6.73-6.99 (m, 9H), 7.11 (d, $J = 7.7$ Hz, 2H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.67 (br s, 1H); MH⁺ at m/z = 475; Anal. Calc'd for C₂₇H₃₀N₄O₄ · HCl · 0.75H₂O: C, 61.83; H, 6.25; N, 10.68. Found: C, 61.82; H, 6.26; N, 10.61.

Compound 30

2-[2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-(3-fluorobenzyl)-3-oxo-2*H*-1,4-benzoxazine



5

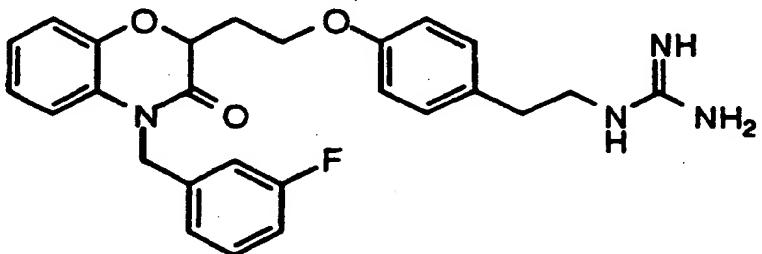
Prepared from 10508-24-A (Reference Example 45) by Method L and isolated as a white foam in 17% yield after chromatography using 20% EtOAc in hexane; IR (KBr) 3330, 2979, 1723, 1688, 1638, 1132, 1059, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.50 (s, 9H), 2.27-2.38 (m, 1H), 2.53-

- 10 2.64 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.64 (q, J = 6.8 Hz, 2H), 4.15-4.29 (m, 2H), 4.94 (dd, J = 9.0, 4.0 Hz, 1H), 5.15 (ABq, J_{AB} = 15.2 Hz, 2H), 6.81-7.04 (m, 8H), 7.13 (d, J = 8.6 Hz, 2H), 7.28-7.92 (m, 2H), 8.36 (t, J = 4.8 Hz, 1H), 11.47 (s, 1H); Anal. Calc'd for C₃₆H₄₃FN₄O₇: C, 65.24; H, 6.54; N, 8.45. Found: C, 65.03; H, 6.43; N, 8.31.

15

Compound 31

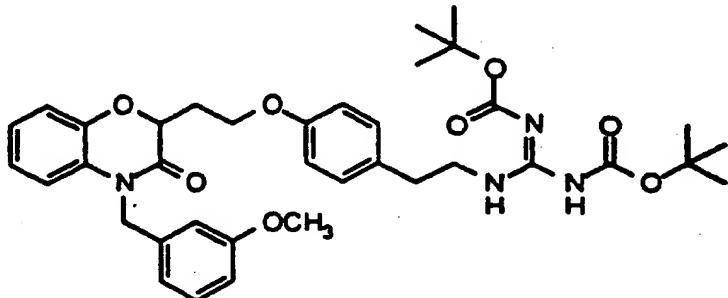
3,4-Dihydro-4-(3-fluorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2*H*-1,4-benzoxazine



- 20 Prepared form Compound 30 by Method K and isolated as a white foam in 97% yield; IR (KBr) 3153, 1654, 1501, 753 cm⁻¹; ¹H NMR (CDCl₃) δ 2.18-2.33 (m, 1H), 2.37-2.52 (m, 1H), 2.78 (br s, 2H), 3.34 (v br s, 2H), 4.05-4.22 (m, 2H), 4.86 (dd, J = 8.7, 4.2 Hz, 1H), 5.07 (s, 2H), 6.75-7.25 (br s, 4H), 6.80 (d, J = 7.6 Hz, 2H), 6.94-7.00 (m, 6H), 7.12 (d, J = 7.7 Hz, 2H), 7.22-7.30 (m, 2H), 7.71 (br s, 1H); Anal. Calc'd for C₂₆H₂₇FN₄O₃·HCl·H₂O·0.1C₃H₈O: C, 60.40; H, 5.94; N, 10.71. Found: C, 60.11; H, 5.86; N, 10.42.

Compound 32

2-[2-[2-[4-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-(3-methoxybenzyl)-3-oxo-2*H*-1,4-benzoxazine



5

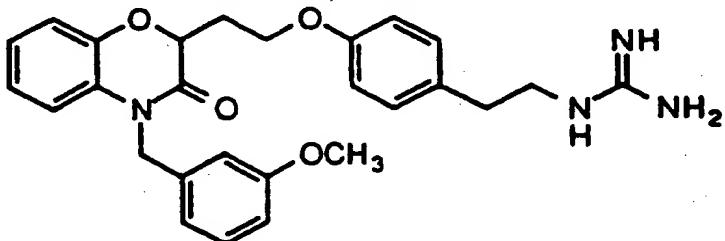
Prepared from intermediate 10508-22-A (Reference Example 76) by Method L and isolated as a white foam in 30% yield; IR (KBr) 3334, 2979, 1723, 1686, 1645, 1615, 1329, 1246, 1156, 1132, 1059, 751 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.26-2.38 (m, 1H), 2.51-2.63 (m, 1H),

10 2.81 (t, $J = 7.2$ Hz, 2H), 3.64 (q, $J = 6.79$ Hz, 2H), 3.77 (s, 3H), 4.15-4.29 (m, 2H), 4.94 (dd, $J = 9.2, 4.0$ Hz, 1H), 5.13 (s, 2H), 6.76-7.02 (m, 8H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.21-7.26 (m, 2H), 8.37 (t, $J = 4.8$ Hz, 1H), 11.47 (s, 1H); Anal. Calc'd for $\text{C}_{37}\text{H}_{46}\text{N}_4\text{O}_8 \cdot 0.1\text{H}_2\text{O}$: C, 65.68; H, 6.88; N, 8.28. Found: C, 65.40; H, 6.83; N, 8.10.

15

Compound 33

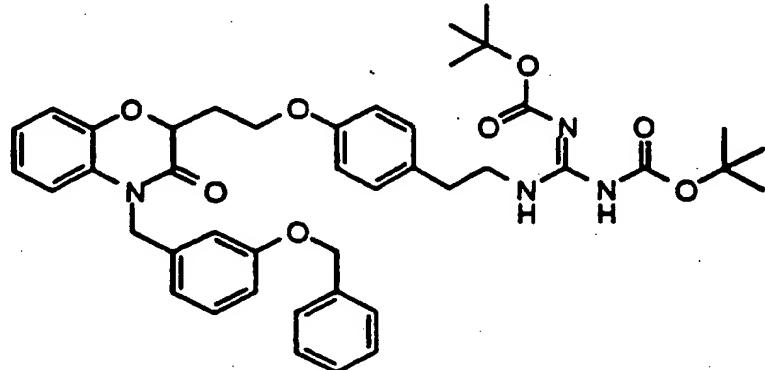
3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-(3-methoxybenzyl)-3-oxo-2*H*-1,4-benzoxazine



20 Prepared from Compound 32 by Method K and isolated as a CHCl_3 soluble white foam in 21% yield; IR (neat) 3020, 1671, 1513, 1501, 1407, 1217, 758 cm^{-1} ; ^1H NMR (CDCl_3) 2.15-2.28 (m, 1H), 2.35-2.48 (m, 1H), 2.70-2.87 (m, 3H), 3.34 (br s, 2H), 3.71 (s, 3H), 4.02-4.17 (m, 2H), 4.85 (dd, $J = 8.8, 4.0$ Hz, 1H), 5.03 (ABq, $J_{AB} = 16.8$ Hz, 2H), 6.72-7.23 (m, 16H), 7.64 (br s, 1H); Anal. Calc'd for $\text{C}_{27}\text{H}_{30}\text{N}_4\text{O}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 61.30; H, 6.29; N, 10.59. Found: C, 61.20; H, 6.04; N, 10.45.

Compound 34

4-(3-Benzylbenzyl)-2-{2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy}ethyl}-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

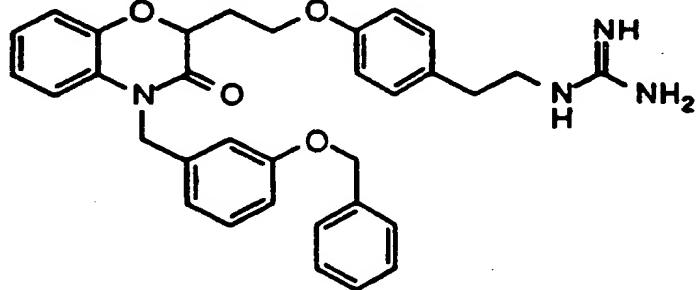


- 5 Prepared from 10508-82-A (Reference Example 77) by Method L and isolated as a white foam in 35% yield after chromatography (eluting with CH₂Cl₂); IR (KBr) 3331, 2977, 1722, 1687, 1638, 1613, 1501, 1410, 1329, 1245, 1156, 1131, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.24-2.37 (m, 1H), 2.50-2.63 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.63 (q, J = 7.1 Hz, 2H), 4.15-4.30 (m, 2H), 4.92 (dd, J = 9.4, 3.9 Hz, 1H), 5.02 (s, 2H), 5.12 (ABq, J_{AB} = 15.4 Hz, 2H), 6.84-7.00 (m, 9H), 7.12 (d, J = 8.6 Hz, 2H), 7.23-7.27 (m, 1H), 7.32-7.42 (m, 5H), 8.37 (br t, J = 4.3 Hz, 1H), 11.5 (s, 1H); Anal. Calc'd for C₄₃H₅₀N₄O₈: C, 68.78; H, 6.71; N, 7.46. Found: C, 68.50; H, 6.78; N, 7.41.

15

Compound 35

4-(3-Benzylbenzyl)-3,4-dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy}ethyl}-3-oxo-2*H*-1,4-benzoxazine



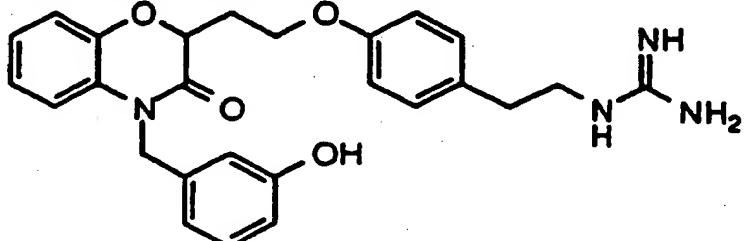
- 20 Prepared from Compound 34 by Method K and isolated as a white foam in 53% yield after repeated ether triturations, mp 100-105°C; IR (KBr) 3338, 3155, 1676, 1610, 1513, 1500, 1400, 1243, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 2.10-2.23 (m, 1H), 2.30-2.44 (m, 1H), 2.74 (br s, 2H), 3.32 (br s, 2H), 3.97-4.15 (m, 2H), 4.81 (dd, J = 8.7, 4.1 Hz, 1H), 4.96 (s, 2H), 5.01 (s, 2H), 6.75-

7.33 (m, 23H), 7.63 (br s, 1H); Anal. Calc'd for C₃₃H₃₄N₄O₄·HCl·H₂O: C, 65.50; H, 6.16; N, 9.26. Found: C, 65.77; H, 5.98; N, 9.06.

Compound 36

5

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-(3-hydroxybenzyl)-3-oxo-2*H*-1,4-benzoxazine

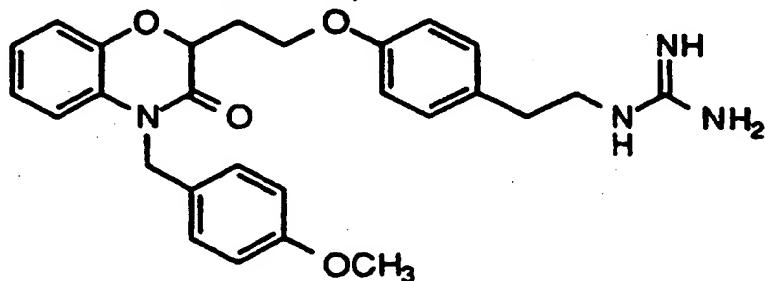


Compound 35 (0.5 g, 0.83 mmol) was reacted with H₂ at 50 psi in a Parr shaker containing 10% Pd/C (200 mg) in MeOH. After 2h, the catalyst was removed and the filtrate was concentrated in vacuum. The product was isolated as a white powder in 40% yield after ether trituration; IR (KBr) 3159, 1661, 1613, 1512, 1500, 1242, 752 cm⁻¹; ¹H NMR (DMSO-*d*₆ plus CDCl₃) δ 2.28-2.38 (m, 1H), 2.45-2.58 (m, 1H), 2.82 (t, J = 7.4 Hz, 2H), 3.01 (s, HDO), 3.40 (q, J = 6.8 Hz, 2H), 4.15-4.30 (m, 2H), 4.91 (dd, J = 9.1, 4.3 Hz, 1H), 5.08 (s, 2H), 6.69-6.75 (m, 3H), 6.87-7.02 (m, 8H), 7.11-7.30 (m, 5H), 7.54 (br t, J = 5.1 Hz, 1H), 9.05 (s, 1H); MH⁺ at m/z = 461; Anal. Calc'd for C₂₆H₂₈N₄O₄·2HCl·H₂O: C, 56.63; H, 5.85; N, 10.16. Found: C, 56.46; H, 5.61; N, 9.85.

20

Compound 37

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-(4-methoxybenzyl)-3-oxo-2*H*-1,4-benzoxazine



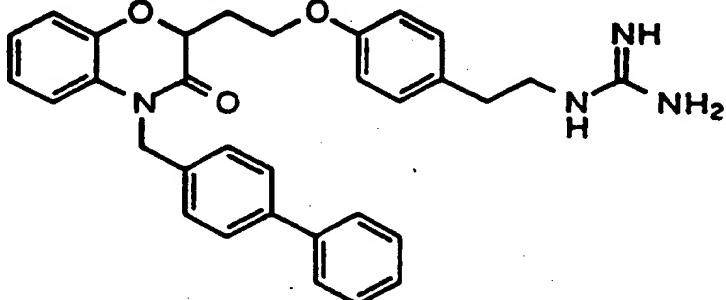
Prepared by method L using intermediate 10508-19 (Reference Example 47) and N,N'-di-1-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K to give a white foam in 53% yield; IR (KBr) 3411, 1654, 1617, 1515, 1501, 1248, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 2.20 (m, 1H), 2.31-2.44 (m, 1H), 2.72 (br t, J = 6.4 Hz, 2H), 3.29 (br t, J = 6.4 Hz, 2H), 3.68 (s, 3H), 3.96-

4.12 (m, 2H), 4.79 (dd, $J = 8.8, 4.0$ Hz, 1H), 4.97 (s, 2H), 6.70-7.30 (v br s, 4H), 6.71-6.93 (m, 8H), 7.05-7.13 (m, 4H), 7.70 (br s, 1H); MH^+ at m/z = 475; Anal. Calc'd for $C_{27}H_{30}N_4O_4 \cdot HCl \cdot H_2O$: C, 61.30; H, 6.29; N, 10.59. Found: C, 61.17; H, 6.10; N, 10.25.

5

Compound 38

3,4-Dihydro-2-[2-{4-(2-guanidinoethyl)phenoxy]ethyl}-3-oxo-4-(4-phenylbenzyl)-2H-1,4-benzoxazine

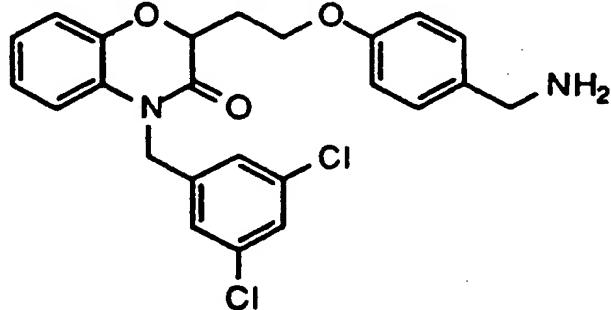


- 10 Prepared by method L using intermediate 11578-99 (Reference Example 59) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and method K to give a white foam in 18% overall yield; IR (KBr) 3157, 1681, 1500, 1398, 1243, 759 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.20-2.33 (m, 1H), 2.38-2.54 (m, 1H), 2.73-2.82 (m, 2H), 3.27-3.39 (m, 2H), 4.05-4.22 (m, 2H), 4.88 (dd, $J = 8.9, 4.4$ Hz, 1H), 5.12 (s, 2H), 6.65-7.57 (v br s, 4H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.88-6.97 (m, 3H), 7.11 (d, $J = 8.3$ Hz, 2H), 7.25-7.32 (m, 4H), 7.39 (t, $J = 7.1$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 4H), 7.71 (br s, 1H); MH^+ at m/z = 521; Calc'd for $C_{32}H_{32}N_4O_3 \cdot HCl \cdot H_2O$: C, 66.83; H, 6.13; N, 9.74. Found: C, 67.01; H, 5.99; N, 9.53.
- 15

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Compound 39

2-[2-{4-(2-Aminomethyl)phenoxy]ethyl}-4-(3,5-dichlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



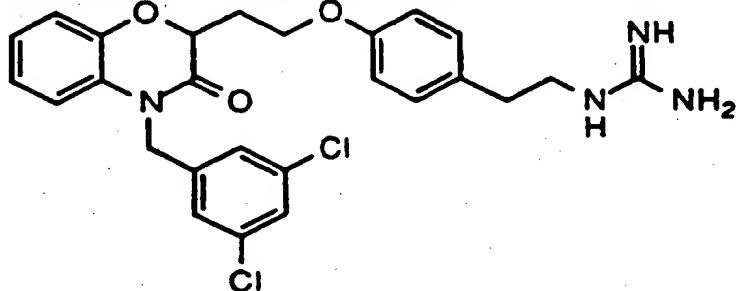
Prepared by method L using intermediate 10005-181-1 (Reference Example 48) and N,N'-*t*-butoxycarbonyl-(4-hydroxyphenyl)benzylamine and method K to give a white solid directly from the reaction in 73% yield, mp 228.5-230 C; IR (KBr) 2927, 1680, 1517, 1503, 1402, 1254, 752 cm⁻¹; ¹H NMR (DMSO-*d*₆)

- 5 δ 2.20-2.31 (m, 1H), 2.36-2.48 (m, 1H), 3.94 (s, 2H), 4.20-4.28 (m, 2H), 5.05 (dd, *J* = 8.5, 3.8 Hz, 1H), 5.18 (ABq, *J*_{AB} = 16.7 Hz, 2H), 6.96-7.10 (m, 6H), 7.35 (d, *J* = 1.8 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.52 (t, *J* = 1.8 Hz, 1H), 8.37 (br s, 3H); Anal. Calc'd for C₂₄H₂₂Cl₂N₂O₃·HCl·0.5H₂O: C, 57.33; H, 4.81; N, 5.57. Found: C, 57.33; H, 4.77; N, 5.37.

10

Compound 40

4-(3,5-Dichlorobenzyl)-3,4-dihydro-
2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-3-oxo-2*H*-1,4-benzoxazine

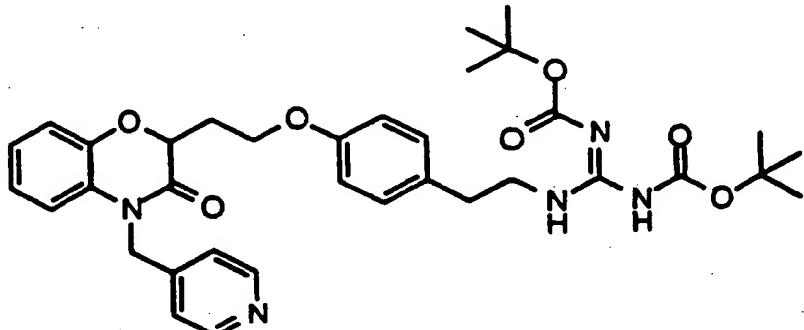


- 15 Prepared by method L using intermediate 10005-181-1 (Reference Example 48) and N,N'-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethylguanidine and method K to give a cream-colored solid in 48% yield, mp 115.5-117°C; IR (KBr) 3328, 1665, 1515, 1501, 1399, 1245, 751 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.17-2.30 (m, 1H), 2.33-2.47 (m, 1H), 2.72 (t, *J* = 7.2 Hz, 2H), 3.28-3.48 (m, 3H), 4.15-4.24 (m, 2H), 5.02-5.06 (m, 1H), 5.18 (ABq, *J*_{AB} = 16.7 Hz, 2H), 6.8-7.6 (v br s, 4H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.99-7.10 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.35 (s, 2H), 7.52 (s, 1H), 7.66 (t, *J* = 5.5 Hz, 1H); Anal. Calc'd for C₂₆H₂₆Cl₂N₄O₃·HCl·0.25H₂O: C, 56.33; H, 5.00; N, 10.11. Found: C, 56.18; H, 5.26; N, 9.90.

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Compound 41

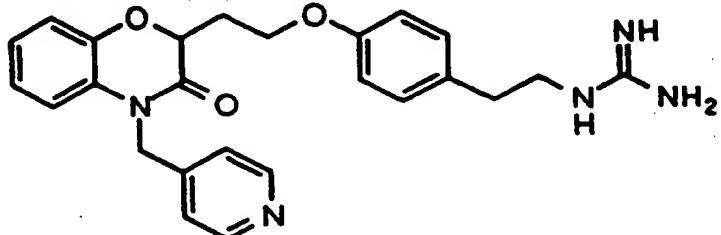
2-{2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy}ethyl}-3,4-dihydro-4-(3-methoxybenzyl)-3-oxo-4-(4-picoly)-2*H*-1,4-benzoxazine



- 5 Prepared by method L using intermediate 10840-22 (Reference Example 58) and *N,N'*-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine to give an off-white powder in 20% yield; IR (KBr) 2979, 1723, 1690, 1638, 1501, 1416, 1368, 1333, 1246, 1158, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.50 (s, 9H), 2.28-2.40 (m, 1H), 2.53-2.64 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.63 (br q, J = 7.2 Hz, 2H), 4.16-4.30 (m, 2H), 4.96 (dd, J = 9.2, 4.0 Hz, 1H), 5.16 (ABq, J_{AB} = 14 Hz, 2H), 6.73 (dd, J = 8.4, 1.5 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.93 (td, J = 7.2, 2.0 Hz, 1H), 6.97-7.06 (m, 2H), 7.12-7.17 (m, 4H), 8.36 (br t, J = 4.8 Hz, 1H), 8.56 (dd, J = 4.5, 1.6 Hz, 2H), 11.47 (s, 1H); Anal. Calc'd for C₃₅H₄₃N₅O₇: C, 65.10; H, 6.71; N, 10.85. Found: C, 64.73; H, 6.69; N, 10.46.

Compound 42

3,4-Dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy}ethyl}-3-oxo-4-(4-picoly)-2*H*-1,4-benzoxazine



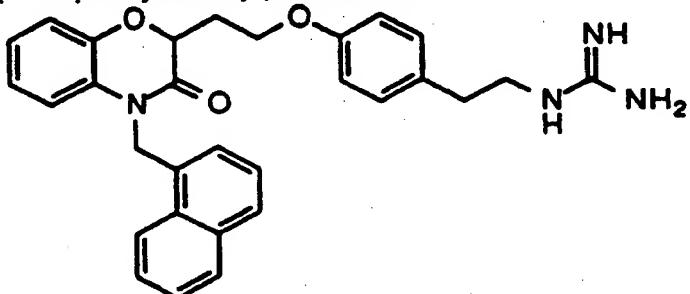
- 20 Prepared from Compound 41 by Method K and isolated as a white solid in 30% yield after trituration with ether, mp 244-248 °C; IR (KBr) 3184, 1673, 1640, 1499, 1403, 1248, 760 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.20-2.35 (m, 1H), 2.35-2.48 (m, 1H), 2.72 (t, J = 7.2 Hz, 2H), 3.32 (q, J = 6.6 Hz, 2H), 3.50-4.50 (v br s, 1H), 4.15-4.26 (m, 2H), 5.07 (dd, J = 8.8, 4.1 Hz, 1H), 5.40 (ABq, J_{AB} = 18.1 Hz, 2H), 6.80-7.55 (v br s, 4H), 6.87-7.13 (m, 6H), 7.21 (d, J = 8.6 Hz,

2H), 7.66 (t, J = 5.6 Hz, 1H), 7.78 (d, J = 6.3 Hz, 2H), 8.78 (d, J = 6.4 Hz, 2H);
 MH⁺ at m/z = 446; Anal. Calc'd for C₂₅H₂₇N₅O₃·2HCl·0.5H₂O: C, 56.93; H,
 5.73; N, 13.28. Found: C, 56.87; H, 5.60; N, 13.06.

5

Compound 43

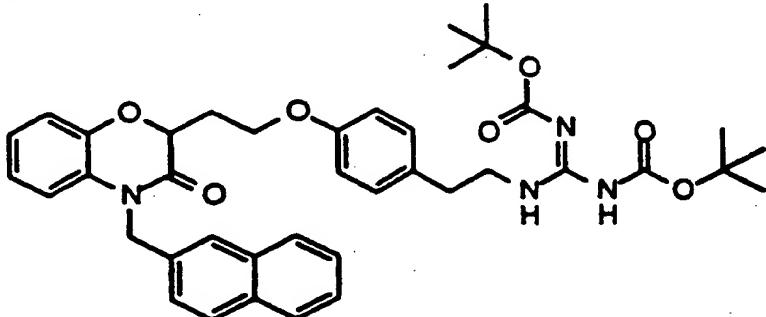
3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-(1-naphthylmethyl)-3-oxo-2H-1,4-benzoxazine



Prepared by method L using intermediate 10508-84-A1 (Reference Example
 10 78) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethylguanidine and
 method K using trifluoroacetic acid with anisole present, instead of IPA/HCl.
 The crude material was treated with CH₂Cl₂/ether to give the title compound
 as a cream-colored solid in 72% yield; m. p. 75-80°C; IR (KBr) 3360, 1671,
 1501, 1405, 1204, 1136, 799, 723 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.29-2.37 (m,
 15 1H), 2.37-2.50 (m, 1H), 2.72 (t, J = 7.4 Hz, 2H), 3.28-3.48 (m, 2H), 3.31-3.39
 (m, 2H), 3.48 (v br s, 1H), 4.16-4.29 (m, 2H), 5.08 (dd, J = 8.8, 4.2 Hz, 1H),
 5.62 (ABq, J_{AB} = 17.4 Hz, 2H), 6.86-7.66 (v br s, 4H), 6.86-7.06 (m, 4H), 7.11
 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.48-7.55
 (m, 1H), 7.58-7.68 (m, 2H), 7.85 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 9.1 Hz), 8.21
 (d, J = 8.1 Hz); MH⁺ at m/z = 495; Anal. Calc'd for C₃₀H₃₀N₄O₃·C₂HF₃O₂: C,
 20 62.38; H, 5.06; N, 9.04. Found: C, 62.38; H, 5.06; N, 9.04.

Compound 44

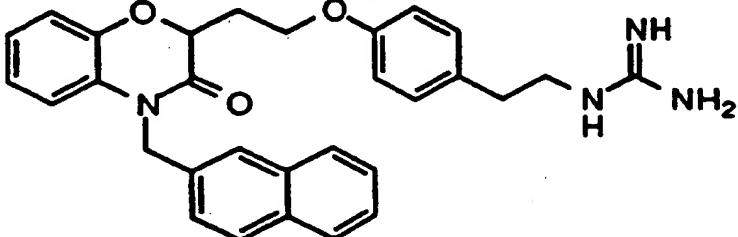
2-[2-[4-[2-(N,N-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-(2-naphthylmethyl)-3-oxo-2*H*-1,4-benzoxazine



- 5 Prepared by method L using intermediate 10508-80-1 (Reference Example 79) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethylguanidine. The crude material was purified by flash chromatography eluting with EtOAc/hexane to afford the product as a white foam in 24% yield; IR (KBr) 3330, 3053, 2977, 2931, 1722, 1638, 1614, 1512, 1501, 1366, 1330, 1244, 1156, 1131, 748 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.31-2.44 (m, 1H), 2.55-2.68 (m, 1H), 2.82 (t, J = 7.1 Hz, 2H), 3.65 (q, J = 6 Hz, 2H), 4.20-4.33 (m, 2H), 5.00 (dd, J = 9.4, 3.4 Hz, 1H), 5.32 (ABq, J_{AB} = 15.4 Hz, 2H), 6.84-6.96 (m, 5H), 7.00 (t, J = 6.8 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.45-7.48 (m, 2H), 7.68 (s, 1H), 7.75-7.83 (m, 3H), 8.20 (br s, 1H), 11.48 (s, 1H); Anal. Calc'd for C₄₀H₄₆N₄O₇: C, 69.14; H, 6.67; N, 8.06. Found: C, 69.16; H, 6.88; N, 7.63.
- 10 1156, 1131, 748 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.31-2.44 (m, 1H), 2.55-2.68 (m, 1H), 2.82 (t, J = 7.1 Hz, 2H), 3.65 (q, J = 6 Hz, 2H), 4.20-4.33 (m, 2H), 5.00 (dd, J = 9.4, 3.4 Hz, 1H), 5.32 (ABq, J_{AB} = 15.4 Hz, 2H), 6.84-6.96 (m, 5H), 7.00 (t, J = 6.8 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.4 Hz, 1H), 7.45-7.48 (m, 2H), 7.68 (s, 1H), 7.75-7.83 (m, 3H), 8.20 (br s, 1H), 11.48 (s, 1H); Anal. Calc'd for C₄₀H₄₆N₄O₇: C, 69.14; H, 6.67; N, 8.06. Found: C, 69.16; H, 6.88; N, 7.63.
- 15 8.20 (br s, 1H), 11.48 (s, 1H); Anal. Calc'd for C₄₀H₄₆N₄O₇: C, 69.14; H, 6.67; N, 8.06. Found: C, 69.16; H, 6.88; N, 7.63.

Compound 45

3,4-Dihydro-2-[2-[4-(2-guanidinylethyl)phenoxy]ethyl]-4-(2-naphthylmethyl)-3-oxo-2*H*-1,4-benzoxazine

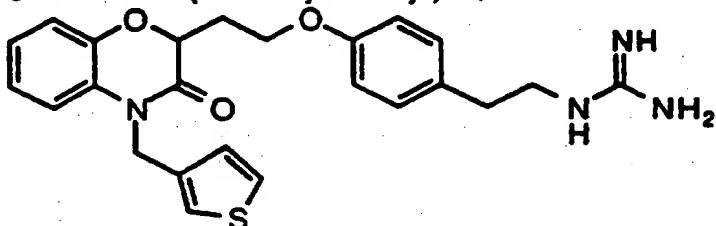


- 20 Prepared from Compound 44 by Method K and triturated with ether to afford the title compound as a white solid in 80% yield, mp 173-178°C; IR (KBr) 3154, 1680, 1501, 1400, 1241, 752 cm⁻¹; ¹H NMR (DMSO-d₆) 2.22-2.35 (m, 1H), 2.38-2.48 (m, 1H), 2.72 (t, J = 7.3 Hz, 2H), 3.28-3.38 (m, 2H), 4.17-4.26 (m, 2H), 5.05 (dd, J = 8.7, 4.0 Hz, 1H), 5.34 (ABq, J_{AB} = 16.2 Hz, 2H), 6.80-
- 25 8.20 (br s, 1H), 11.48 (s, 1H); Anal. Calc'd for C₄₀H₄₆N₄O₇: C, 69.14; H, 6.67; N, 8.06. Found: C, 69.16; H, 6.88; N, 7.63.

7.80 (v br s, 4H), 6.92-7.01 (m, 4H), 7.08 (t, $J = 7.3$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.48-7.51 (m, 2H), 7.59 (br t, $J = 5.1$ Hz, 1H), 7.78 (s, 1H), 7.83-7.91 (m, 3H); MH^+ at m/z = 495; Anal. Calc'd for $C_{30}H_{30}N_4O_3 \cdot HCl \cdot 0.7H_2O$: C, 66.28; H, 6.01; N, 10.31. Found: C, 66.30; H, 5 5.88; N, 10.06.

Compound 46

3,4-Dihydro-2-{2-[4-(2-guanidinylethyl)phenoxy]ethyl}-
3-oxo-2H-4-(3-thienylmethyl)-1,4-benzoxazine

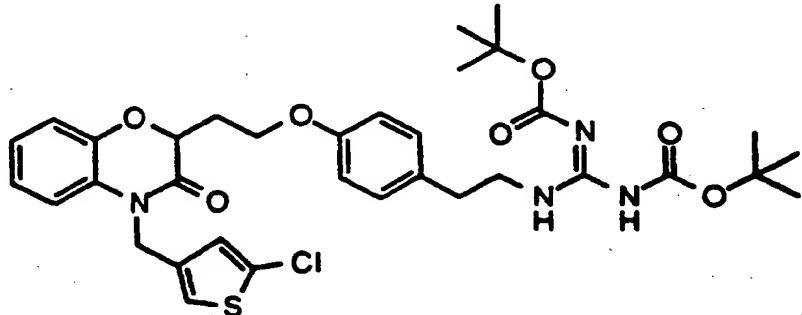


10

Prepared by method L using intermediate 11721-108-1 (Reference Intermediate 85) and N,N'-di-t-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine and method K using trifluoroacetic acid with anisole present, instead of IPA/HCl. The crude product was purified by flash chromatography using 1% MeOH in CH_2Cl_2 to 6% MeOH/1% NH_4OH in CH_2Cl_2 , and isolated in 48% yield as a tan foam, mp 66-71°C; IR (KBr) 3364, 1655, 1500, 1246, 1203, 1136, 751 cm⁻¹; ¹H NMR ($DMSO-d_6$) δ 2.11-2.26 (m, 1H), 2.3-2.43 (m, 1H), 2.73 (t, $J = 6.9$ Hz, 2H), 3.28-3.39 (m, 1H), 4.13-4.22 (m, 2H), 4.93 (dd, $J = 8.8, 4.1$ Hz, 1H), 5.12 (ABq, $J_{AB} = 17.2$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 3H), 6.99-7.04 (m, 5H), 7.12-7.22 (m, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 2.3$ Hz, 1H), 7.52 (dd, $J = 4.6, 2.3$ Hz, 1H), 7.62 (t, $J = 5.75$ Hz, 1H); MH^+ at m/z = 451; Anal. Calc'd for $C_{24}H_{26}N_4O_3S \cdot C_2HF_3O_2$: C, 51.61; H, 4.39; N, 8.85. Found: C, 51.34; H, 4.60; N, 8.85.

Compound 47

2-[2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(2-chloro-4-thienylmethyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

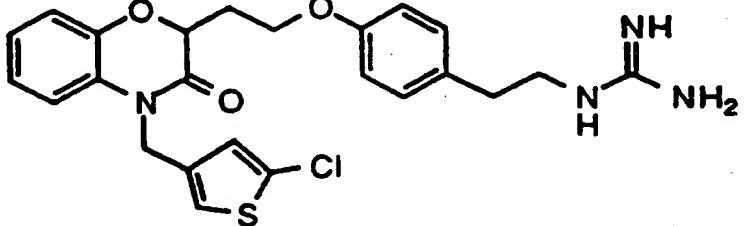


- 5 Prepared from 10508-79 (Reference Example 80) by method L using equal equivalents of reagents to starting material and isolated as a white foam in 24% yield; IR (KBr) 3330, 2978, 1722, 1686, 1638, 1615, 1500, 1413, 1331, 1247, 1130, 1058, 748 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.20-2.32 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.60-3.66 (m, 2H), 4.12-4.28 (m, 2H), 4.78 (dd, J = 9.3, 4.0 Hz, 1H), 5.16 (ABq, J_{AB} = 15.8 Hz, 2H), 6.75 (d, J = 3.8 Hz, 1H), 6.82-6.85 (m, 3H), 7.00-7.08 (m, 4H), 7.12 (d, J = 8.6 Hz, 2H), 8.37 (t, J = 3.5 Hz, 1H), 11.47 (s, 1H); Anal. Calc'd for C₃₄H₄₁CIN₄O₇S: C, 59.60; H, 6.03; N, 8.18. Found: C, 59.27; H, 6.02; N, 8.01.
- 10

15

Compound 48

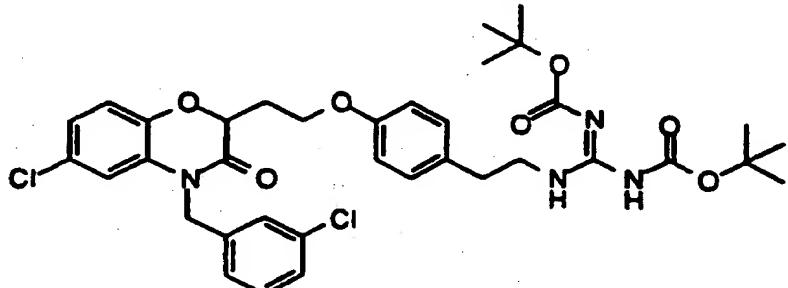
4-(2-Chloro-4-thienylmethyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2*H*-1,4-benzoxazine



- Prepared from Compound 47 by method K in 88% crude yield. This crude material was leached with EtOAc to remove the impurities to afford the product as a white foam; IR (KBr) 3148, 1667, 1500, 1450, 1399, 1243, 1058, 749 cm⁻¹; ¹H NMR (CDCl₃) δ 2.04-2.23 (m, 3H), 2.30-2.41 (m, 1H), 2.72-2.83 (m, 2H), 3.28-3.40 (m, 2H), 3.97-4.15 (m, 2H), 4.77 (dd, J = 7.7, 3.4 Hz, 1H), 5.06 (ABq, J_{AB} = 14.5 Hz, 2H), 6.69-7.20 (v br s, 4H), 6.69-6.80 (m, 3H), 6.92-7.06 (m, 5H), 7.11 (d, J = 8.1 Hz, 2H), 7.64 (br s, 1H); Anal. Calc'd for C₂₄H₂₅CIN₄O₃S·HCl·H₂O: C, 53.43; H, 5.23; N, 10.39. Found: C, 53.08; H, 5.27; N, 10.32.
- 20
- 25

Compound 49

2-[2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-6-chloro-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine



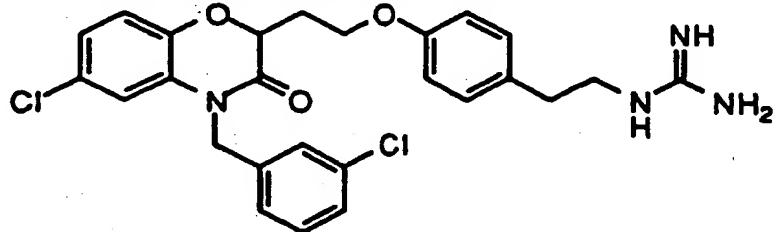
5

Prepared from 11578-71 (Reference Example 49) by Method L using equal equivalents of reagents to starting material and isolated in 34% yield as a colorless oil after chromatography (eluting with CH₂Cl₂); IR (neat) 3332, 2978, 1721, 1694, 1638, 1615, 1498, 1415, 1367, 1132, 811, 777 cm⁻¹; ¹H

- 10 NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.25-2.37 (m, 1H), 2.54-2.66 (m, 1H), 2.82 (t, J = 7.2 Hz, 2H), 3.63 (q, J = 5.6 Hz, 2H), 4.16-4.25 (m, 2H), 4.94 (dd, J = 9.3, 3.9 Hz, 1H), 5.09 (ABq, J_{AB} = 16.1 Hz, 2H), 6.80 (s, 1H), 6.85 (d, J = 8.5 Hz, 2H), 6.95 (s, 2H), 7.13 (d, J = 8.5 Hz, 3H), 7.23-7.31 (m, 3H), 8.37 (br t, J = 2Hz, 1H), 11.47 (s, 1H); Anal. Calc'd for C₃₆H₄₂Cl₂N₄O₇: C, 60.59; H, 5.93; N, 7.85. Found: C, 60.65; H, 6.04; N, 7.65.

Compound 50

6-Chloro-4-(3-chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine



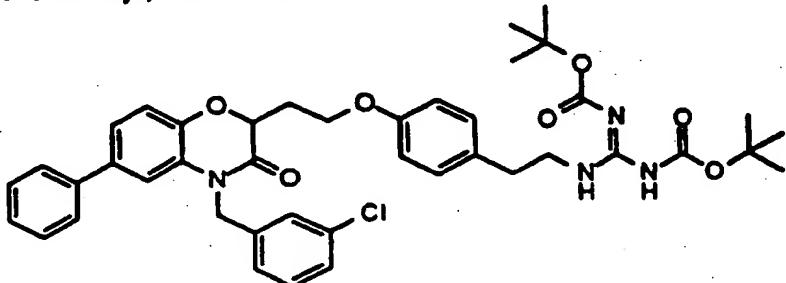
20

Prepared from Compound 49 by Method K where the product was isolated as a white foam from CH₂Cl₂ in 28% yield; IR (KBr) 3154, 1684, 1668, 1496, 1376, 1264, 1243, 1092 cm⁻¹; ¹H NMR (CDCl₃) δ 2.13-2.27 (m, 1H), 2.35-2.50 (m, 1H), 2.74 (br s, 2H), 3.31 (br s, 2H), 4.00-4.14 (m, 2H), 4.84 (dd, J = 9.0, 4.2 Hz, 1H), 4.98 (ABq, J_{AB} = 17.5 Hz, 2H), 6.73-7.29 (m, 15H), 7.61 (br s, 1H); MH⁺ at m/z = 513; Anal. Calc'd for

$C_{26}H_{26}Cl_2N_4O_3 \cdot HCl \cdot 0.7H_2O \cdot 0.2C_3H_8O$: C, 55.61; H, 5.26; N, 9.75. Found:
C, 55.83; H, 5.01; N, 9.51.

Compound 51

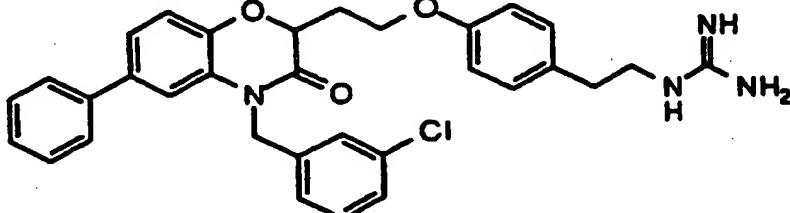
- 5 2-[2-{4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy}ethyl]-
4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-6-phenyl-2*H*-1,4-benzoxazine



Prepared from 11578-41 (Reference Example 44) by Method L and isolated
as an oil in 46% yield. This material was crystallized from ether/hexane to
10 afford a white crystalline solid, mp 115-116°C; IR (KBr) 2976, 2931, 1724,
1689, 1642, 1614, 1430, 1336, 1135, 766 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s,
9H), 1.50 (s, 9H), 2.30-2.43 (m, 1H), 2.35-2.46 (m, 1H), 2.81 (t, J = 7.3 Hz,
2H), 3.63 (q, J = 7.1 Hz, 2H), 4.17-4.32 (m, 2H), 4.99 (dd, J = 9.3, 3.9 Hz, 1H),
5.18 (ABq, J_{AB} = 25.7 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 7.04-7.40 (m, 14H),
15 8.38 (t, J = 4.3 Hz, 1H), 11.47 (br s, 1H); Anal. Calc'd for C₄₂H₄₇ClN₄O₇: C,
66.79; H, 6.27; N, 7.42. Found: C, 66.49; H, 6.20; N, 7.34.

Compound 52

- 20 4-(3-Chlorobenzyl)-3,4-dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-
3-oxo-6-phenyl-2*H*-1,4-benzoxazine

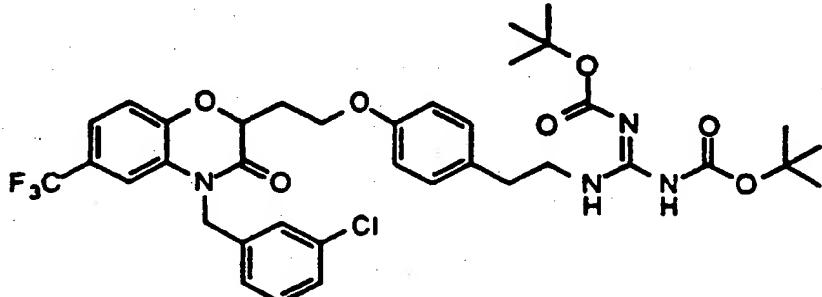


Prepared from Compound 51 by Method K and isolated as a yellow powder
in 20% yield; IR (KBr) 3149, 1666, 1609, 1512, 1241, 1076, 1051, 761 cm⁻¹;
¹H NMR (CD₃OD) δ 2.31-2.40 (m, 1H), 2.43-2.54 (m, 1H), 2.81 (t, J = 7.2 Hz,
2H), 3.41 (t, J = 7.0 Hz, 2H), 4.20-4.31 (m, 2H), 4.85 (s, 5H plus CD₃OH),
25 4.99 (dd, J = 11.1, 4.5 Hz, 1H), 5.28 (s, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.08 (d,
J = 8.3 Hz, 1H), 7.12-7.43 (m, 13H); Anal. Calc'd for

$C_{32}H_{31}ClN_4O_3 \cdot HCl \cdot 1.4H_2O$: C, 62.32; H, 5.69; N, 9.08. Found: C, 61.95; H, 5.51; N, 9.27.

Compound 53

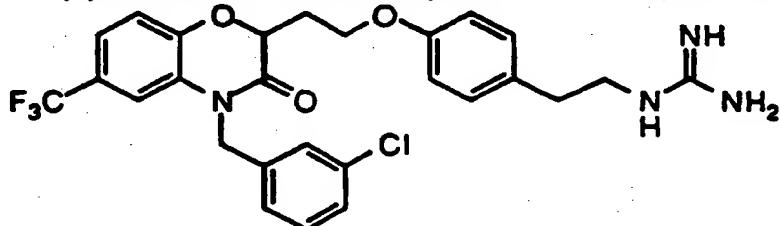
- 5 2-{2-[4-[2-(*N,N'*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy}ethyl}-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-6-trifluoromethyl-2*H*-1,4-benzoxazine



Prepared from 11578-56 (Reference Example 50) by method L using equal equivalents of reagents and isolated as a colorless oil in 18% yield after
 10 SiO_2 column chromatography (CH_2Cl_2); IR (KBr) 3333, 2979, 1723, 1696, 1639, 1617, 1453, 1330, 1303, 1165, 1129, 824 cm^{-1} ; 1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.26-2.40 (m, 1H), 2.55-2.67 (m, 1H), 2.82 (t, J = 7.1 Hz, 2H), 3.63 (q, J = 5.4 Hz, 2H), 4.06-4.27 (m, 2H), 5.02 (dd, J = 9.2, 3.9 Hz, 1H), 5.14 (ABq, J_{AB} = 16.1 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 7.05-7.17 (m, 3H), 7.13 (d, J = 8.5 Hz, 2H), 7.23-7.30 (m, 4H), 8.37 (br t, J = 4.3 Hz, 1H), 11.48 (s, 1H); Anal. Calc'd for $C_{37}H_{42}ClF_3N_4O_3$: C, 59.48; H, 5.67; N, 7.50. Found: C, 59.60; H, 5.67; N, 7.39.

Compound 54

- 20 4-(3-Chlorobenzyl)-3,4-dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]-ethyl}-3-oxo-6-trifluoromethyl-2*H*-1,4-benzoxazine



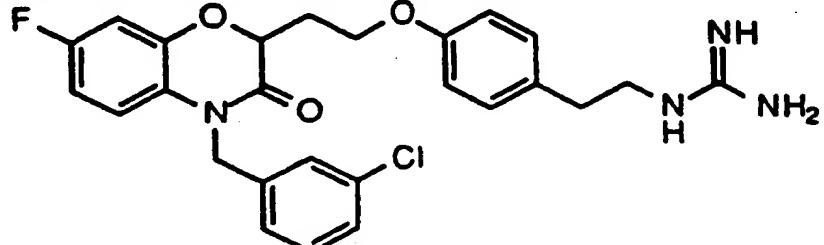
Prepared from Compound 53 by Method K and isolated as a white foam in 27% yield; IR (KBr) 3336, 3159, 1667, 1453, 1304, 827 cm^{-1} ; 1H NMR ($CDCl_3$) δ 2.20-2.39 (m, 1H), 2.48 (br s, 3H), 2.77 (br s, 2H), 3.35 (br s, 2H), 4.08 (br s, 2H), 4.93 (dd, J = 8.6, 4.0 Hz, 1H), 5.06 (ABq, J_{AB} = 16.8 Hz, 2H), 6.75-7.30 (v br s, 4H), 6.77 (d, J = 7.7 Hz, 2H), 7.01-7.26 (m, 7H), 7.25 (d, J =

7.1 Hz, 2H), 7.64 (v br s, 1H); MH⁺ at m/z = 547; Anal. Calc'd for C₂₇H₂₆ClF₃N₄O₃·HCl·0.7H₂O: C, 54.41; H, 4.80; N, 9.40. Found: C, 54.49; H, 4.74; N, 9.32.

5

Compound 55

4-(3-Chlorobenzyl)-3,4-dihydro-7-fluoro-
2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-3-oxo-2H-1,4-benzoxazine

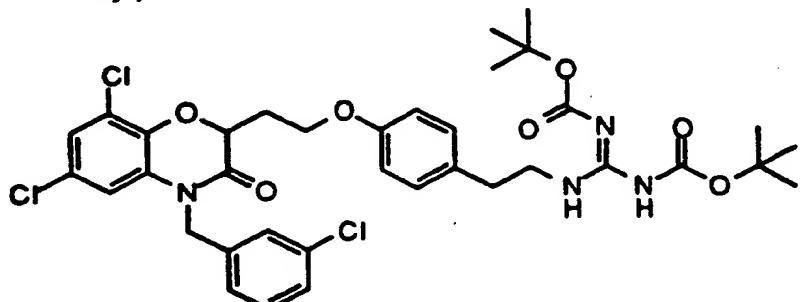


Prepared from 11578-47 (Reference Example 52) and N,N'-di-1-
10 butoxycarbonyl-2(4-hydroxyphenyl)ethylguanidine by Method L using equal
equivalents of reagents and by Method K. The product was isolated in 17%
overall yield as a white foam; IR (KBr) 2877, 1664, 1509, 1405, 1243, 1154,
852 cm⁻¹; ¹H NMR (CD₃OD) 2.26-2.37 (m, 1H), 2.42-2.53 (m, 1H), 2.83 (t, J =
6.8 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 4.17-4.29 (m, 2H), 4.84 (s, 6.4H plus
15 CD₃OH), δ 4.98 (dd, J = 8.4, 4.4 Hz, 1H), 5.18 (s, 2H), 6.73 (td, J = 8.8, 2.6
Hz, 1H), 6.83 (dd, J = 9.2, 2.8 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 6.97 (dd, J =
8.8, 5.2 Hz, 1H), 7.17 (d, J = 8 Hz, 2H), 7.17-7.22 (m, 1H), 7.25-7.35 (m, 3H);
MH⁺ at m/z = 497; Anal. Calc'd for C₂₆H₂₆ClFN₄O₃·HCl·0.7H₂O: C, 57.19;
H, 5.24; N, 10.26. Found: C, 56.81; H, 5.36; N, 10.26.

20

Compound 56

2-{2-[4-[2-(N,N'-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl}-
4-(3-chlorobenzyl)-6,8-dichloro-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



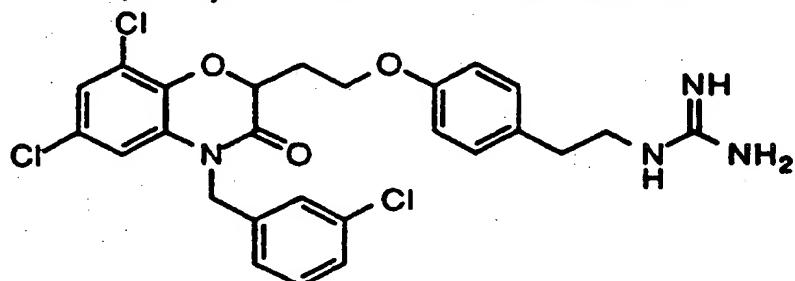
25 Prepared from 11578-33 (Reference Example 56) and N,N'-di-1-
butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine by Method L using equal
equivalents of reagents to starting material and isolated as white solid in

27% yield after SiO₂ column chromatography eluting with CH₂Cl₂, mp 115-117°C; IR (KBr) 2977, 1699, 1639, 1615, 1593, 1367, 1131, 1058, 810, 776 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.51 (s, 9H), 2.25-2.37 (m, 1H), 2.52-2.67 (m, 1H), 2.82 (t, J = 7.2 Hz, 2H), 3.63 (q, J = 7.1 Hz, 2H), 4.13-4.24 (m, 1H), 4.27-4.35 (m, 1H), 5.05 (dd, J = 9.7, 3.5 Hz, 1H), 5.10 (s, 2H), 6.71 (d, J = 2.2 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 8.6 Hz, 2H), 7.13 (s, 1H), 7.26-7.29 (m, 3H), 8.37 (t, J = 2.6 Hz, 1H), 11.48 (s, 1H); Anal. Calc'd for C₃₆H₄₁Cl₃N₄O₇: C, 57.80; H, 5.52; N, 7.49. Found: C, 57.64; H, 5.39; N, 7.77.

10

Compound 57

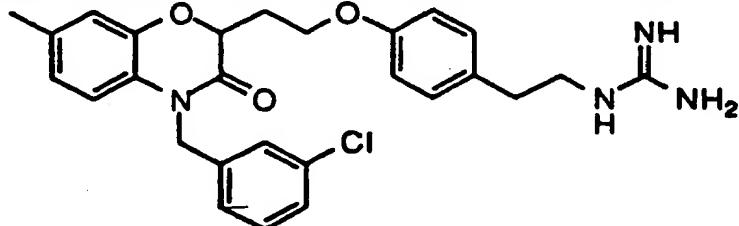
4-(3-Chlorobenzyl)-6,8-dichloro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



15 Prepared from Compound 56 by method K and isolated as a white foam in 75% yield; IR (KBr) 3150, 1666, 1591, 1479, 1242, 743 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.23-2.37 (m, 1H), 2.50-2.61 (m, 1H), 2.84 (t, J = 7.1 Hz, 2H), 3.39 (q, J = 5.9 Hz, 2H), 4.15-4.23 (m, 1H), 4.25-4.35 (m, 1H), 5.04 (dd, J = 9.8, 3.8 Hz, 1H), 5.11 (ABq, J_{AB} = 16.3 Hz, 2H), 6.75 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 7.07-7.21 (m, 9H), 7.26-7.35 (m, 2H), 7.67 (br t, J = 5.1 Hz, 1H); MH⁺ at m/z = 547; Anal. Calc'd for C₂₆H₂₅Cl₃N₄O₃·HCl·0.7H₂O: C, 52.31; H, 4.63; N, 9.39. Found: C, 52.37; H, 4.59; N, 9.37.

Compound 58

25 **4-(3-Chlorobenzyl)-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-3,4-dihydro-7-methyl-3-oxo-2H-1,4-benzoxazine**

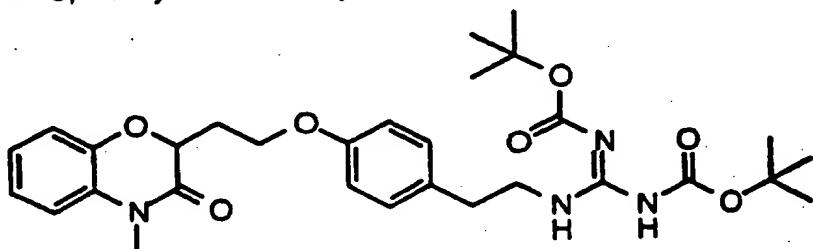


Prepared by method L using intermediate 11578-52 (Referenced Example 55) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethylguanidine and method K in 2.5% overall yield as a white foam; IR (KBr) 3340, 3161, 1668, 1402, 1244, 1178, 1146, 1107, 1056 cm⁻¹; ¹H NMR (CDCl₃) δ 2.15-2.28 (m, 1H), 2.20 (s, 3H), 2.34-2.47 (m, 3H), 2.76 (t, J = 6.4 Hz, 2H), 3.30-3.40 (m, 2H), 4.00-4.18 (m, 2H), 4.83 (dd, J = 8.9, 4.3 Hz, 1H), 5.01 (s, 2H), 6.63-7.27 (v br s, 4H), 6.63-6.70 (m, 2H), 6.75-6.83 (m, 2H), 7.03-7.23 (m, 7H), 7.63 (br s, 1H); MH⁺ at m/z = 493; Anal. Calc'd for C₂₇H₂₉CIN₄O₃·HCl·H₂O: C, 59.23; H, 5.89; N, 10.23. Found: C, 58.84; H, 5.60; N, 10.07.

10

Compound 59

2-[2-[4-[2-(N,N'-Bis-*t*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine

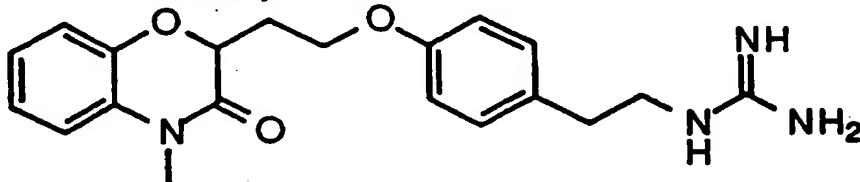


15 Prepared from 10840-117-1 (Reference Example 88) by Method L and isolated as a white foam in 13% yield; IR (KBr) 3334, 2978, 2933, 1722, 1686, 1639, 1614, 1513, 1504, 1417, 1131, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.50 (s, 9H), 2.19-2.31 (m, 1H), 2.45-2.56 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.38 (s, 3H), 3.63 (q, J = 5.3 Hz, 2H), 4.10-4.26 (m, 2H), 4.83 (dd, J = 8.8, 4.0 Hz, 1H), 6.84 (d, J = 6.84 Hz, 2H), 6.95-7.07 (m, 4H), 7.12 (d, J = 8.6 Hz, 2H), 8.36 (br t, J = 4.0 Hz, 1H), 11.47 (s, 1H); Anal. Calc'd for C₃₀H₄₀N₄O₇·0.2H₂O: C, 62.96; H, 7.12; N, 9.79. Found: C, 62.88; H, 7.20; N, 9.71.

25

Compound 60

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-methyl-3-oxo-2*H*-1,4-benzoxazine



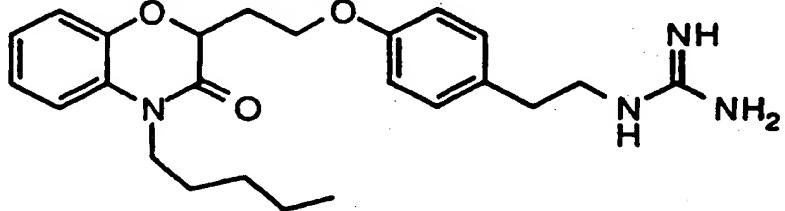
Prepared by dissolving Compound 59 in CH₂Cl₂ and treating with TFA. Solvent removal and purification by SiO₂ chromatography (2-6% MeOH in CH₂Cl₂) followed by crystallization from MeOH/CH₂Cl₂/ether afforded an 82% yield of a cream colored solid, mp 80 ° (shrinks) 82-85 C; IR (KBr)

5 3339, 3176, 1682, 1515, 1505, 1383, 1249, 1137, 755 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.08-2.16 (m, 1H), 2.27-2.33 (m, 1H), 2.71 (t, J = 7.5 Hz, 2H), 3.27-3.35 (m, 2H), 3.30 (s, 3H), 4.10-4.18 (m, 2H), 4.81 (dd, J = 8.8, 4.2 Hz, 1H), 6.83-7.50 (v br s, 4H), 6.90 (d, J = 8.6 Hz, 2H), 7.00-7.12 (m, 4H), 7.18 (d, J = 8.7 Hz, 2H), 7.56 (br t, J = 5.7 Hz, 1H); MH⁺ at m/z = 369.

10

Compound 61

3,4-Dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-
3-oxo-4-pentyl-2H-1,4-benzoxazine

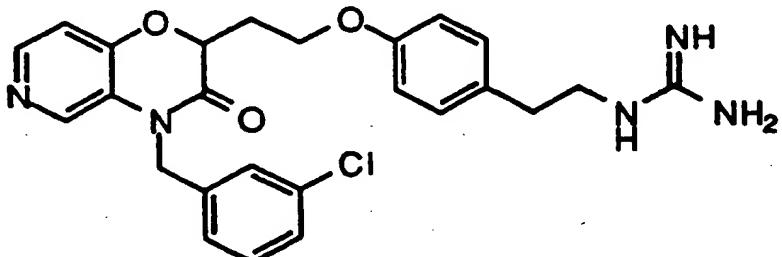


15 Prepared from intermediate 10840-185 (Reference Example 60) by Method K and isolated as a colorless glass in 98% yield; IR (KBr) 3154, 1661, 1513, 1500, 1244, 751 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, J = 6.5 Hz, 3H), 1.19 (d, isopropanol), 1.25-1.37 (m, 4H), 1.52-1.68 (m, 2H), 2.09-2.21 (m, 1H), 2.30-2.40 (m, 1H), 2.79 (br s, 2H), 3.38 (br s, 2H), 3.84 (t, J = 6.7 Hz, 2H), 4.00-4.15 (m, 2H plus isopropanol), 4.71 (dd, J = 8.7, 4.0 Hz, 1H), 6.70-7.17 (v br s, 4H), 6.78 (d, J = 7.5 Hz, 2H), 6.93-7.07 (m, 4H), 7.13 (d, J = 7.4, 2H), 7.67 (br d, 1H); MH⁺ at m/z = 425; Anal. Calc'd for C₂₄H₃₂N₄O₃ · HCl · 0.1C₃H₈O · 0.6H₂O: C, 61.00; H, 7.38; N, 11.73. Found: C, 61.04; H, 7.27; N, 11.67.

20

Compound 62

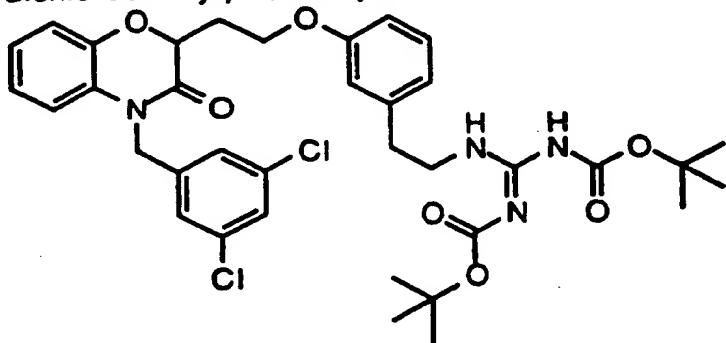
4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-pyrido[4,3-b]-1,4-oxazine



- 5 Prepared by method L using intermediate 11578-190 (Reference Example 84) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine and method K in 35% as an off-white foam; IR (KBr) 3134, 1701, 1669, 1642, 1508, 1240, 1178, 1161, 1055, 824 cm⁻¹; ¹H NMR (DMSO-d₆) δ 2.50 (m, 1H plus DMSO-d₅), 2.71 (t, J = 7.5 Hz, 2H), 3.28-3.35 (m, 3H), 4.17 (t, J = 5.6 Hz, 2H), 5.25 (ABq, J_{AB} = 16.5 Hz, 2H), 5.52 (t, J = 6.9, 1H), 6.70-7.60 (v br s, 5H), 6.83 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.28-7.40 (m, 3H), 7.48 (s, 1H), 7.50 (s, 1H), 7.67 (t, J = 5.4 Hz, 1H), 8.39 (s, 1H), 8.40 (s, 1H); MH⁺ at m/z = 480; Anal. Calc'd for C₂₅H₂₆CIN₅O₃·2HCl·1.5H₂O: C, 51.78; H, 5.39; N, 12.08. Found: C, 51.78; H, 5.39; N, 12.08.
- 10
- 15

Compound 63

2-[2-[3-[2-(N,N-Bis-*t*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(3,5-dichlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



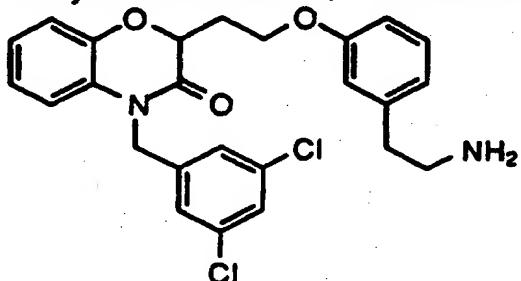
- 20 Prepared from 10005-181-1 (Reference Example 48) by Method L and isolated in 84% yield as a white solid after flash chromatography eluting with 2.5-10% EtOAc in CH₂Cl₂ and crystallization from CH₂Cl₂/ether/hexane, mp 116-118°C; IR (KBr) 3359, 1688, 1505, 1256, 1171, 752 cm⁻¹; ¹H NMR (CDCl₃) δ 1.44 (s, 9H), 2.28-2.39 (m, 1H), 2.52-2.62 (m, 1H), 2.77 (t, J = 9Hz, 2H), 3.33-3.41 (m, 2H), 4.16-4.30 (m, 2H), 4.54 (br s, 1H), 4.94 (dd, J = 10.5,
- 25

3 Hz, 1H), 5.09 (ABq, $J_{AB} = 18$ Hz, 2H), 6.75-6.83 (m, 4H), 6.93-7.06 (m, 3H), 7.13 (d, $J = 1.8$ Hz, 2H), 7.20-7.27 (m, 2H); Anal. Calcd for $C_{30}H_{32}Cl_2N_2O_5$: C, 63.05; H, 5.64; N, 4.90. Found: C, 63.24; H, 5.60; N, 4.71.

5

Compound 64

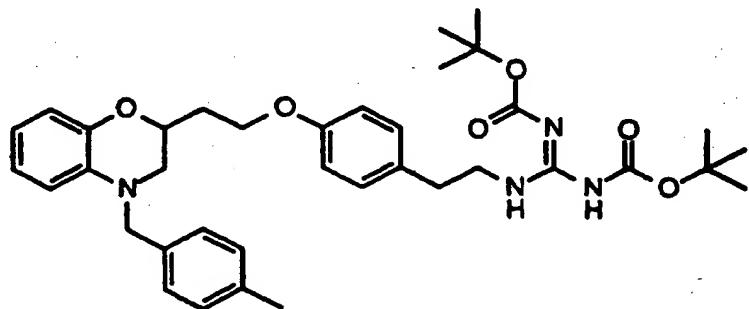
2-[2-[3-(2-Aminoethyl)phenoxy]ethyl]-4-(3,5-dichlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared by methods J using intermediate 10005-181-1 (Reference Example 48) and 4-[2-(N-1-butoxycarbonylamino)ethyl]phenol as well as method K to give a white solid, 58% yield. mp 173.5-176°C; IR (KBr) 2942, 1684, 1592, 1501, 1399, 1265, 752 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 2.19-2.32 (m, 1H), 2.35-2.47 (m, 1H), 3.84-3.89 (m, 2H), 3.01-3.06 (m, 2H), 4.19-4.24 (m, 2H), 5.03-5.08 (m, 1H), 5.18 (ABq, $J_{AB} = 16.7$ Hz, 2H), 6.83-6.87 (m, 3H), 6.99-7.09 (m, 4H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 1.8$ Hz, 2H), 7.52 (t, $J = 1.8$ Hz, 1H), 8.06 (br s, 3H); Anal. Calcd for $C_{25}H_{24}Cl_2N_2O_3 \cdot HCl \cdot 0.25 H_2O$: C, 58.61; H, 5.02; N, 5.47. Found: C, 58.47; H, 4.88; N, 5.33.

Compound 65

20 2-[2-[4-[2-(*N,N'*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-(4-methylbenzyl)-2H-1,4-benzoxazine

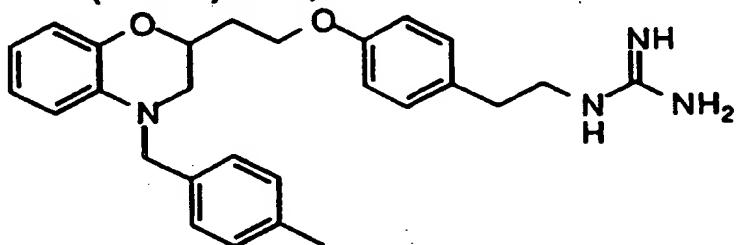


Intermediate 10840-45 (1 eq, Reference Example 92) was dissolved in 7 mL CH₂Cl₂/ether (3/1) under nitrogen and treated with triethylamine (1.2 eq) followed by methanesulfonyl chloride (1.2 eq). The mixture was stirred for 0.5 h and filtered. The filtrate was concentrated under vacuum and the

residue was redissolved in ether and washed with H₂O and dried over MgSO₄. Ether removal produced the desired methanesulfonate product. This crude material (1 eq) was dissolved in DMSO (1.7 mL) and treated with the corresponding phenol (1 eq) plus NaOH pellets (3 eq). This solution was stirred at 50°C for 24 h under nitrogen and then diluted with H₂O. A CH₂Cl₂/EtOAc solution of the precipitate was washed with H₂O and dried over MgSO₄. Solvent removal produced the crude material which was purified by flash chromatography to afford the product in 16% overall yield and isolated as a white powder; IR (KBr) 2979, 1723, 1650, 1625, 1513, 1246, 1156, 1133, 743 cm⁻¹; ¹H NMR (CDCl₃) δ 1.47 (s, 9H), 1.50 (s, 9H), 2.03-2.17 (m, 2H), 2.33 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.18 (dd, J = 11.9, 7.2 Hz, 1H), 3.34 (dd, J = 11.9, 2.5, 1H), 3.63 (q, J = 6.8 Hz, 2H), 4.08-4.23 (m, 2H), 4.38-4.45 (m, 3H), 6.62 (dt, J = 7.5, 1.5 Hz, 1H), 6.69 (dd, J = 7.5, 1.5 Hz, 1H), 6.75-6.84 (m, 2H), 6.82 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.16 (br q, J_{AB} = 8.1 Hz, 4H), 8.36 (br t, J = 4.8 Hz, 1H), 11.46 (s, 1H); Anal. Calc'd for C₃₇H₄₈N₄O₆: C, 68.92; H, 7.50; N, 8.69. Found: C, 68.65; H, 7.24; N, 8.56.

Compound 66

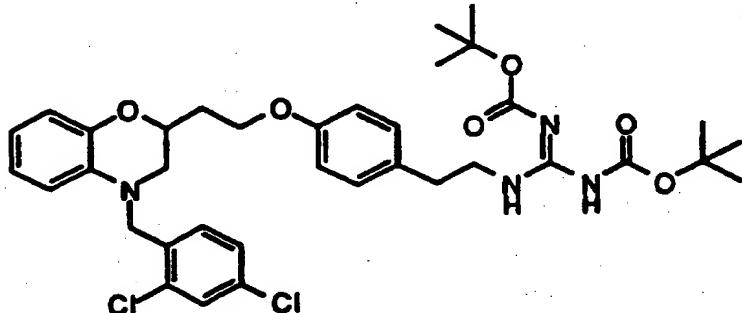
20 3,4-Dihydro-2-{2-[4-[2-guanidinoethyl]phenoxy]ethyl}-4-(4-methylbenzyl)-2H-1,4-benzoxazine



Prepared from Compound 65 by Method K in 3% yield and isolated as a green powder after trituration with CHCl₃; IR (KBr) 3157, 1663, 1611, 1513, 1300, 1241, 743 cm⁻¹; ¹H NMR (CD₃OD) δ 2.04-2.14 (m, 2H), 2.30 (s, 3H), 2.81 (t, J = 7.2 Hz, 2H), 3.18 (dd, J = 12.0, 8.0 Hz, 1H), 3.36-3.49 (m, 3H), 4.07-4.2 (m, 2H), 4.37-4.46 (m, 1H), 4.50 (s, 2H), 6.70-6.95 (m, 7H), 7.05-7.40 (m, 9H); Anal. Calc'd for C₂₇H₃₂N₄O₂·HCl·1.75H₂O: C, 63.37; H, 7.31; N, 11.26. Found: C, 63.40; H, 7.14; N, 11.21.

Compound 67

2-[2-[4-[2-(*N,N*'-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(2,4-dichlorobenzyl)-3,4-dihydro-2*H*-1,4-benzoxazine

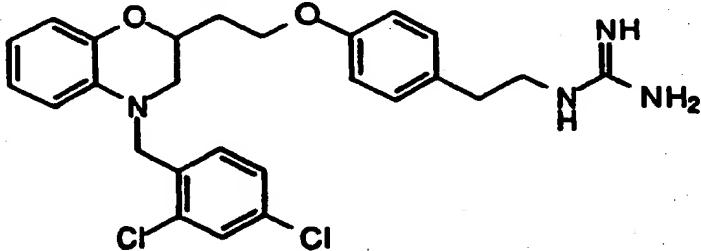


- 5 Prepared from 10840-8 (Reference Example 94) by Method L in 20% yield and isolated as a white foam; IR (KBr) 3336, 2979, 2932, 1723, 1640, 1617, 1366, 1133 cm⁻¹; ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.50 (s, 9H), 2.08-2.20 (m, 2H), 2.81 (t, J = 7.2 Hz, 2H), 3.31 (dd, J = 11.7, 7.5 Hz, 1H), 3.41 (dd, J = 11.6, 2.6 Hz, 1H), 3.64 (q, J = 6.5 Hz, 2H), 4.10-4.27 (m, 2H), 4.44-4.53 (m, 1H), 4.46 (s, 2H), 6.45 (dd, J = 8.0, 1.3 Hz, 1H), 6.65 (td, J = 7.6, 1.4 Hz, 1H), 6.76 (td, J = 7.8, 1.6 Hz, 1H), 6.80-6.87 (m, 3H), 7.10-7.24 (m, 4H), 7.42 (d, J = 1.9 Hz, 1H), 8.35 (t, J = 4.1 Hz, 1H), 11.46 (s, 1H); Anal. Calc'd for C₃₆H₄₄Cl₂N₄O₆·0.5H₂O: C, 61.01; H, 6.40; N, 7.91. Found: C, 61.14; H, 6.37; N, 7.83.
- 10

15

Compound 68

(2,4-Dichlorobenzyl)-3,4-dihydro-2-[4-(2-guanidinoethyl)phenoxy]ethyl]-4-2*H*-1,4-benzoxazine

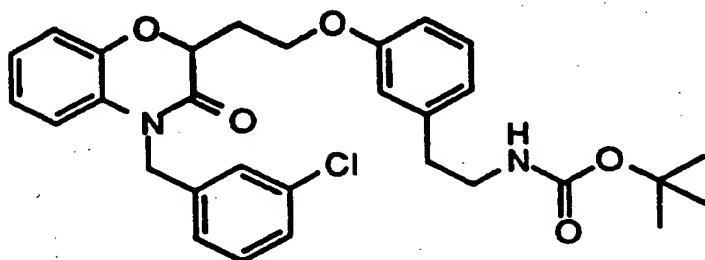


- 20 Prepared from Compound 67 by Method K in 4.5% yield and isolated as a green glass; IR (neat) 3334, 3166, 1665, 1611, 1513, 1246, 1219, 1046, 830 cm⁻¹; ¹H NMR (CDCl₃) δ 1.74 (br s, 2H), 1.94-2.15 (m, 2H), 2.80 (br t, J = 5.6 Hz, 2H), 3.20-3.38 (m, 4H), 4.02-4.18 (m, 2H), 4.32-4.47 (m, 1H), 4.42 (s, 2H), 6.35-7.40 (v br s, 4H), 6.41 (dd, J = 8.0, 1.1 Hz, 1H), 6.61 (td, J = 7.6, 1.2 Hz, 1H), 6.73 (td, J = 7.9, 1.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 2H), 7.10-7.20 (m, 5H), 7.39 (d, J = 1.8 Hz, 1H), 7.80 (br s, 1H); MH⁺ at m/z = 499; Anal. Calc'd
- 25

for $C_{26}H_{28}Cl_2N_4O_2 \cdot HCl \cdot H_2O$: C, 56.38; H, 5.64; N, 10.11. Found: C, 56.68; H, 5.41; N, 9.97.

Compound 69

- 5 2-[2-[3-(2-(1-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-
-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

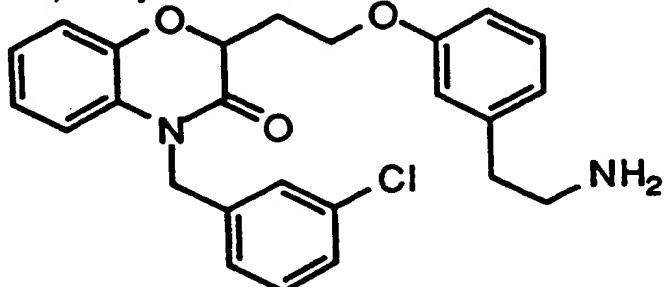


Prepared from 10488-22 (Reference Example 66) and 3-[2-(N-1-butoxycarbonylamino)ethyl]phenol by method J. The product was isolated in 10 82% yield after chromatography, to afford an oil which crystallized on standing, mp 107-108°C; MS (Cl) MH^+ no peak found; IR (KBr) 3319, 2986, 1597, 1532, 1505, 1468, 1445, 1402, 1368, 1323, 1271, 1171, 1061, 787, 752 cm^{-1} ; 1H NMR ($CDCl_3$) δ 7.23 (m, 5H), 7.13 (m, 1H), 7.00 (m, 2H), 6.94 (m, 1H), 6.78 (m, 3H), 5.18 (d, 1H, J = 16.0 Hz), 5.08 (d, 1H, J = 16.0 Hz), 4.94 (dd, 1H, J = 3.9, 9.2 Hz), 4.55 (br. s., 1H), 4.24 (m, 2H), 3.38 (m, 2H), 2.76 (t, 2H, J = 6.9 Hz), 2.58 (m, 1H), 2.34 (m, 1H), 1.43 (s, 9H). Anal. Calc'd for 15 $C_{30}H_{33}ClN_2O_5 \cdot 0.4H_2O$: C 66.28, H 6.26, N 5.15. Found: C 66.28, H 6.13, N 5.02.

20

Compound 70

- 2-[2-[3-(2-Aminoethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-
-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

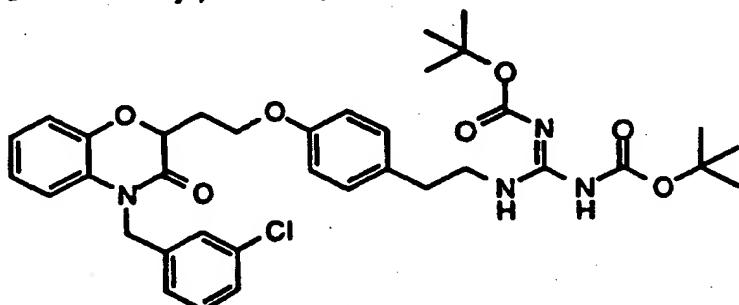


25 Prepared from Compound 69 by method K in quantitative yield, mp: 163 C
darkens, 169-171°C melts; MS (Cl) MH^+ 437; IR (KBr) 2948, 1678, 1599, 1503, 1468, 1447, 1402, 1321, 1265, 1171, 1115, 1051, 939, 866 cm^{-1} ; 1H

NMR (DMSO-*d*₆) δ 8.80-8.00 (v br s, 2H), 7.22 (m, 4H), 7.10 (m, 1H), 6.95 (m, 3H), 6.80 (m, 4H), 5.13 (d, 1H, *J* = 16.3Hz), 5.05 (d, 1H, *J* = 16.3Hz), 4.89 (dd, 1H, *J* = 3.8, 8.8Hz), 4.19 (m, 2H), 3.28 (br s, 2H), 3.08 (br s, 2H), 2.49 (m, 1H), 2.27 (m, 1H), 2.52-1.50 (v br s, 1H). Anal. Calc'd for C₂₅H₂₅ClN₂O₃ · HCl: C 63.43, H 5.54, N 5.92. Found: C 63.16, H 5.40, N 5.73.

Compound 71

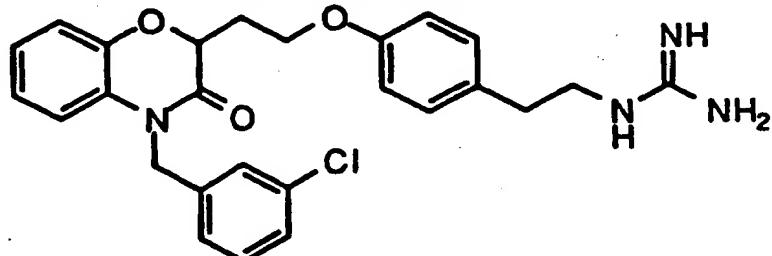
2-[2-[4-[2-(*N,N'*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-2*H*-1,4-benzoxazine



10 Prepared from 10488-22 (Reference Example 66) and *N,N'*-di-*tert*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine by method J in 31% yield, mp: 74-78°C; MS (FAB) MH⁺679; IR (KBr) 3332, 2979, 1723, 1688, 1501, 1414, 1368, 1329, 1246, 1132, 1059, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 11.47 (br s, 1H), 8.36 (br t, 1H), 7.25 (s, 2H), 7.14 (d, 2H, *J* = 3.7 Hz), 7.06 (m, 2H), 6.92 (m, 4H), 6.84 (m, 2H), 5.19 (d, 1H, *J* = 16.0 Hz), 5.08 (d, 1H, *J* = 16.0 Hz), 4.94 (dd, 1H, *J* = 3.9, 9.3 Hz), 4.22 (m, 2H), 3.63 (m, 2H), 2.81 (t, 2H, *J* = 7.2 Hz), 2.58 (m, 1H), 2.34 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₃ClN₄O₇ · 0.4 H₂O: C 62.99, H 6.43, N 8.16. Found: C 62.96, H 6.37, N 8.09.

Compound 72

4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-2*H*-1,4-benzoxazine



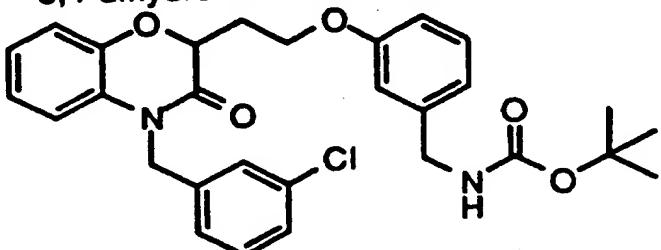
25 Prepared from Compound 71 by method K in 34% yield, mp 90-101°C; IR (KBr) 3355, 1501, 1468, 1402, 1244, 750 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 7.68

(br t, 1H), 7.50-6.80(v br s, 1H), 7.35 (d, 1H, $J = 7.3\text{Hz}$), 7.20 (m, 4H), 7.03 (m, 4H), 6.92 (d, 2H, $J = 8.4\text{Hz}$), 5.22 (d, 1H, $J = 16.5\text{Hz}$), 5.13 (d, 1H, $J = 16.5\text{Hz}$), 5.00 (dd, 1H, $J = 4.2, 8.7\text{Hz}$), 4.21 (m, 2H), 2.72 (br t, 2H), 2.51 (m, 2H), 2.38 (br s, 1H), 2.24 (br s, 1H). Anal. Calc'd for $C_{26}H_{27}ClN_4O_3 \cdot 2.5\text{H}_2O$: C 54.77, H 5.22, N 9.83. Found: C 54.99, H 5.34, N 9.79.

5 HCl: C 54.77, H 5.22, N 9.83. Found: C 54.99, H 5.34, N 9.79.

Compound 73

2-[2-[3-(*t*-Butoxycarbonylaminomethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

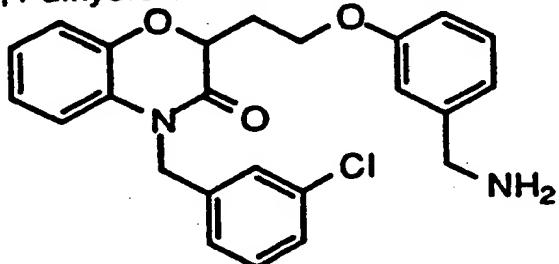


10 Prepared from 10488-22 (Reference Example 66) by method J in 48% yield, mp 98-100°C; MS (Cl) $M+522$, one Cl present; IR (KBr) 3351, 2927, 1599, 1530, 1505, 1447, 1402, 1279, 1175, 1111, 1055, 939, 864 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.24 (m, 5H), 7.13 (m, 1H), 7.00 (m, 2H), 6.92 (m, 1H), 6.83 (m, 3H), 5.18 (d, 1H, $J = 16.0\text{Hz}$), 5.07 (d, 1H, $J = 16.0\text{Hz}$), 4.93 (dd, 1H, $J = 3.9, 9.2\text{Hz}$), 4.83 (br. s, 1H), 4.37-4.14 (brm, 4H), 2.58 (m, 1H), 2.34 (m, 1H), 1.46 (s, 9H). Anal. Calc'd for $C_{29}H_{31}ClN_2O_5 \cdot 0.3\text{H}_2O$: C 65.92, H 6.03, N 5.30. Found: C 65.95, H 5.99, N 5.22.

20

Compound 74

2-[2-[3-(Aminomethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine



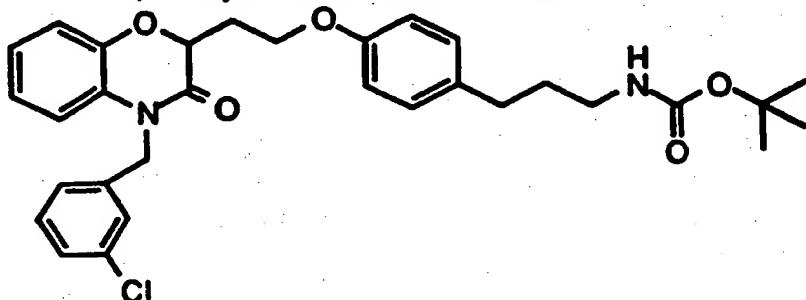
25 Prepared from Compound 73 by method K in quantitative yield, mp 124-129 C; MS (Cl) MH^+423 ; IR (KBr) 2886, 1599, 1501, 1402, 1265, 1171, 1080, 1051, 885, 470 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 7.27 (m, 5H), 7.13 (m, 1H), 7.00 (m, 2H), 6.95 (m, 2H), 6.90 (m, 2H), 6.83 (m, 2H), 5.17 (d, 1H, $J = 16.0\text{Hz}$), 4.83 (br. s, 1H), 4.37-4.14 (brm, 4H), 2.58 (m, 1H), 2.34 (m, 1H), 1.46 (s, 9H). Anal. Calc'd for $C_{29}H_{31}ClN_2O_5 \cdot 0.3\text{H}_2O$: C 65.92, H 6.03, N 5.30. Found: C 65.95, H 5.99, N 5.22.

16.2Hz), 5.08 (d, 1H, $J = 16.2\text{Hz}$), 4.94 (dd, 1H, $J = 4.0, 9.2\text{Hz}$), 4.26 (m, 2H), 3.82 (s, 2H), 2.59 (m, 1H), 2.34 (m, 1H). Anal. Calc'd for $\text{C}_{24}\text{H}_{23}\text{ClN}_2\text{O}_3 \cdot \text{HCl}$ 0.4 H_2O : C 61.78, H 5.36, N 6.00. Found: C 61.78, H 5.36, N 5.83.

5

Compound 75

2-[2-[4-(3-(1-Butoxycarbonylamino)propyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine

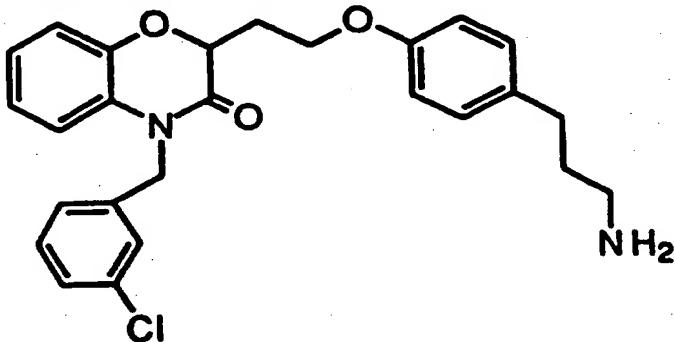


Prepared from 10488-22 (Reference Example 66) and 4-[3-(N-1-butoxycarbonylamino)propyl]phenol by method L in 58% yield, mp 75-81°C; 10 MS (FAB) $\text{MH}^+ 551$; IR (KBr) 3365, 2979, 2934, 1611, 1512, 1503, 1468, 1398, 1366, 1302, 1279, 1242, 1022, 997, 922 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.24 (d, 4H, $J = 6.4\text{Hz}$), 7.12 (m, 2H), 7.08 (d, 1H, $J = 8.6\text{Hz}$), 7.00 (m, 2H), 6.92 (m, 1H), 6.84 (m, 2H), 5.17 (d, 1H, $J = 16.0\text{Hz}$), 5.08 (d, 1H, $J = 16.0\text{Hz}$), 4.94 (dd, 1H, $J = 3.9, 9.2\text{Hz}$), 4.21 (m, 2H), 3.14 (m, 2H), 2.59 (m, 2H), 2.32 (m, 1H), 1.78 (m, 2H), 1.44 (s, 9H). Anal. Calc'd for $\text{C}_{30}\text{H}_{33}\text{ClN}_2\text{O}_5$: C 67.09, H 6.19, N 5.22. Found: C 67.46, H 6.54, N 4.93.

20

Compound 76

2-[2-[4-(3-Aminopropyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine



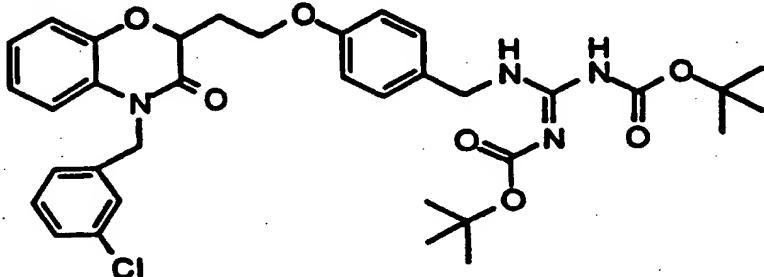
Prepared from Compound 75 by meth d K, mp 109-111°C; MS (Cl) $\text{MH}^+ 451$; IR (KBr) 2936, 1674, 1609, 1514, 1466, 1400, 1302, 1111, 1049, 800, 681 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 7.95 (brs, 2H), 7.36 (m, 4H), 7.21 (d,

25 800, 681 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 7.95 (brs, 2H), 7.36 (m, 4H), 7.21 (d,

1H, $J = 6.8\text{Hz}$), 7.13 (d, 2H, $J = 8.5\text{Hz}$), 7.02 (m, 4H), 6.90 (d, 2H, $J = 8.5\text{Hz}$),
 5.19 (d, 1H, $J = 16.2\text{Hz}$), 5.13 (d, 1H, $J = 16.2\text{Hz}$), 5.00 (dd, 1H, $J = 4.2$,
 8.7Hz), 4.19 (m, 2H), 2.75 (brs, 2H), 2.58 (brt, 2H, $J = 7.4\text{Hz}$), 2.39 (m, 1H).
 5 Anal.Calc'd for $\text{C}_{26}\text{H}_{27}\text{ClN}_2\text{O}_3 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C
 61.78, H 5.98, N 5.54. Found: C 61.91, H 6.07, N 5.62.

Compound 77

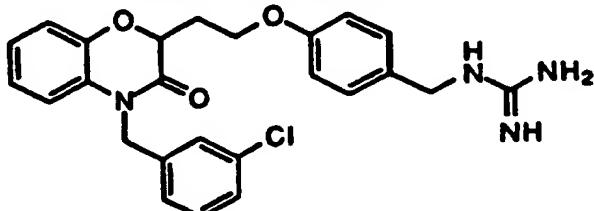
2-[2-[4-[(N,N'-Bis-*tert*-butoxycarbonyl)guanidinomethyl]phenoxy]ethyl]-
 4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine



10 Prepared by method L using intermediate 10488-22 (Reference Example
 66) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)methyl guanidine in
 52% yield, mp 74°C shrinks, 89-95°C melts; MS (FAB) $\text{MH}^+ 665$; IR (KBr)
 15 3334, 2979, 1723, 1690, 1501, 1396, 1368, 1325, 1248, 1057, 810 cm^{-1} ; ^1H
 NMR (CDCl_3) δ 11.52 (s, 1H), 8.49 (br t, 1H), 7.24 (m, 4H), 7.13 (m, 1H), 6.99
 (m, 3H), 6.92 (m, 2H), 6.89 (d, 1H, $J = 8.5\text{Hz}$), 6.82 (d, 1H, $J = 7.5\text{Hz}$), 5.18 (d,
 1H, $J = 16.0\text{Hz}$), 5.08 (d, 1H, $J = 16.0\text{Hz}$), 4.93 (dd, 1H, $J = 3.9, 9.3\text{Hz}$), 4.54
 (d, 2H, $J = 4.9\text{Hz}$), 4.25 (m, 2H), 2.59 (m, 1H), 2.34 (m, 1H), 1.52 (s, 9H), 1.47
 (s, 9H). Anal. Calc'd for $\text{C}_{35}\text{H}_{41}\text{ClN}_4\text{O}_7 \cdot \text{H}_2\text{O}$: C 61.53, H 6.34, N 8.20.
 20 Found: C 61.50, H 6.26, N 8.03.

Compound 78

4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(guanidinylmethyl)phenoxy]ethyl]-
 2*H*-1,4-benzoxazine



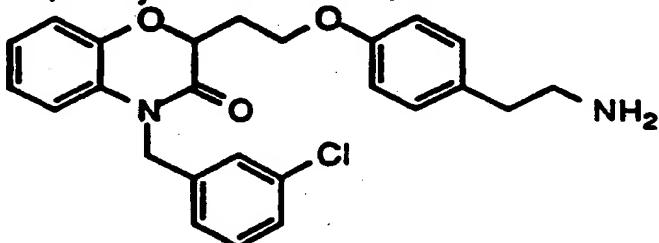
25 Prepared from Compound 77 by method K in 37% yield, mp decomposes
 >61 C; MS (CI) $\text{MH}^+ 465$; IR (KBr) 3338, 1501, 1398, 1246, 1051, 750 cm^{-1} ;
 1H NMR ($\text{DMSO}-d_6$) δ 8.03 (br t, 1H, $J = 5.9\text{Hz}$), 7.35 (m, 5H), 7.23 (m, 5H),

7.02 (m, 6H), 5.23 (d, 1H, $J = 16.5\text{Hz}$), 5.12 (d, 1H, $J = 16.5\text{Hz}$), 5.00 (dd, 1H, $J = 4.2, 8.7\text{Hz}$), 4.29 (d, 2H, $J = 5.9\text{Hz}$), 4.22 (m, 2H), 2.40 (m, 1H), 2.25 (m, 1H). Anal. Calc'd for $\text{C}_{25}\text{H}_{25}\text{ClN}_4\text{O}_3 \cdot \text{HCl} \cdot \text{H}_2\text{O} \cdot 0.1\text{C}_6\text{H}_{14}$: C 58.23, H 5.61, N 10.61. Found: C 58.51, H 5.40, N 10.81.

5

Compound 79

2-[2-[4-(2-Aminoethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

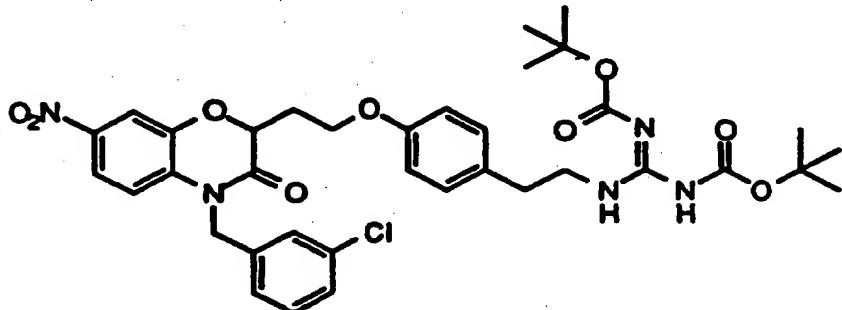


- 10 Prepared from 10488-22 (Reference Example 66) and 4-[2-(N-t-butoxycarbonylamino)ethyl]phenol by method J followed by method K in quantitative yield mp 140.5-143°C; MS (CI) $\text{MH}^+ 437$; IR (KBr) 2930, 1885, 1591, 1503, 1466, 1437, 1398, 1323, 1182, 1138, 991, 879 cm^{-1} ; ^1H NMR (DMSO- d_6) δ 8.00 (br s, 3H), 7.35 (m, 3H), 7.20 (m, 3H), 7.03 (m, 4H), 6.92 (d, 2H, $J = 8.6\text{Hz}$), 5.23 (d, 1H, $J = 16.5\text{Hz}$), 5.13 (d, 1H, $J = 16.4\text{Hz}$), 5.00 (dd, 1H, $J = 4.2, 8.7\text{Hz}$), 4.19 (m, 2H), 2.98 (m, 2H), 2.82 (m, 2H), 2.39 (m, 1H), 2.22 (m, 1H). Anal. Calc'd for $\text{C}_{25}\text{H}_{25}\text{ClN}_2\text{O}_3 \cdot \text{HCl}$: C 63.43, H 5.54, N 5.92. Found: C 63.26, H 5.46, N 5.86.
- 15

20

Compound 80

2-[2-[4-(2-(N,N'-Bis-*t*-butoxycarbonylguanidino)ethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-7-nitro-3-oxo-2H-1,4-benzoxazine



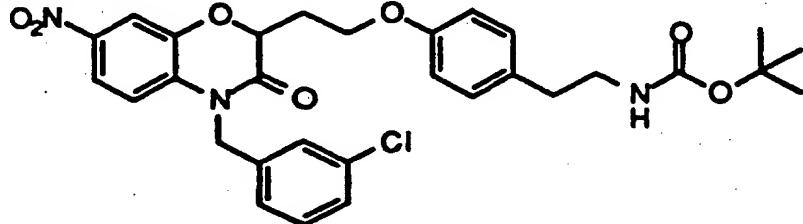
- 25 Prepared from intermediate 11653-35B (Reference Example 87) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidin by method J in 57% yield, mp (dec) >69°C; MS (FAB) $\text{MH}^+ 724$; IR (KBr) 3329, 3119, 3090,

2977, 2933, 2420, 2287, 1575, 1475, 1080, 1057, 927, 855, 701, 576, 490
 cm^{-1} ; ^1H NMR (CDCl_3) δ 11.50 (br s, 1H), 8.37 (br s, 1H), 7.88 (d, 1H, $J = 2.4\text{Hz}$), 7.82 (dd, 1H, $J = 2.6, 8.8\text{Hz}$), 7.28 (d, 2H, $J = 5.1\text{Hz}$), 7.22 (s, 1H), 7.12 (m, 3H), 6.90 (d, 1H, $J = 8.8\text{Hz}$), 6.84 (d, 2H, $J = 8.5\text{Hz}$), 5.23 (d, 1H, $J = 16.4\text{Hz}$), 5.13 (d, 1H, $J = 16.3\text{Hz}$), 5.06 (dd, 1H, $J = 3.4, 9.1\text{Hz}$), 4.23 (m, 2H), 3.63 (q, 2H, $J = 5.4\text{Hz}$), 2.82 (t, 2H, $J = 7.2\text{Hz}$), 2.65 (m, 1H), 2.37 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for $\text{C}_{36}\text{H}_{42}\text{ClN}_5\text{O}_9 \cdot 0.5\text{H}_2\text{O}$: C 58.97, H 5.91, N 9.55. Found: C 58.97, H 6.00, N 9.25.

10

Compound 81

2-[2-[4-[2-(tert-Butoxycarbonylamino)ethyl]phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-7-nitro-3-oxo-2H-1,4-benzoxazine

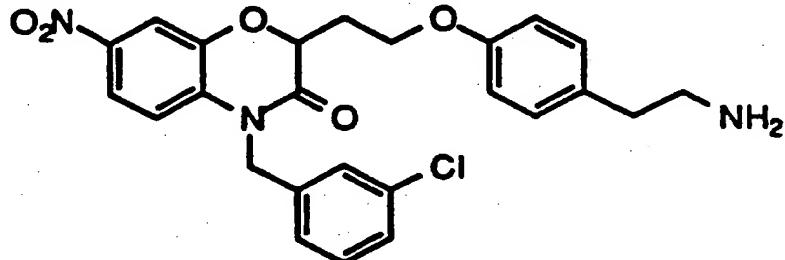


Prepared from intermediate 11653-35B (Reference Example 87) and N,N'-di-1-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine by method J in 20% yield, mp 82-85°C; MS (Cl) $\text{MH}^+ 582$; IR (KBr) 3366, 3085, 2975, 2935, 1882, 1695, 1600, 1526, 1512, 1477, 1442, 1389, 1365, 1301, 1114, 999, 853, 665 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.88 (d, 1H, $J = 2.42\text{ Hz}$), 7.84 (dd, 1H, $J = 8.82, 2.55\text{ Hz}$), 7.28 (m, 4H), 7.22 (s, 1H), 7.12 (d, 2H, $J = 8.57\text{ Hz}$), 6.90 (d, 1H, $J = 8.84\text{ Hz}$), 6.85 (d, 1H, $J = 8.60\text{ Hz}$), 5.23 (d, 1H, $J = 16.2\text{ Hz}$), 5.13 (d, 1H, $J = 16.3\text{ Hz}$), 5.06 (dd, 1H, $J = 9.03, 3.94\text{ Hz}$), 4.53 (br s, 1H), 4.24 (m, 2H), 3.33 (m, 2H), 2.74 (t, 2H, $J = 6.86\text{ Hz}$), 2.62 (m, 1H), 2.37 (m, 1H), 1.44 (s, 9H). Anal. Calc'd for $\text{C}_{30}\text{H}_{34}\text{ClN}_3\text{O}_7$: C 61.91, H 5.54, N 7.22. Found: C 61.58, H 5.80, N 7.36.

25

Compound 82

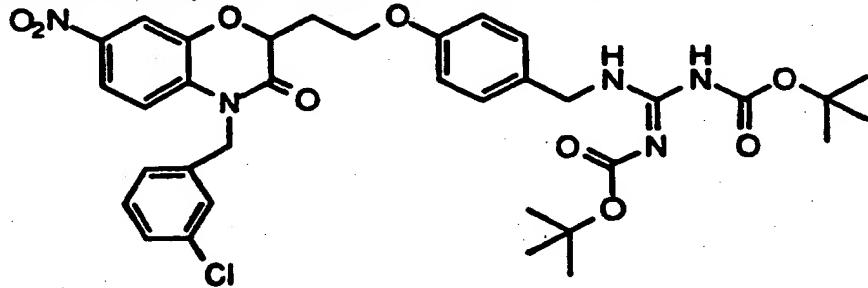
2-(2-[4-(2-Aminoethyl)phenoxy]ethyl)-4-(3-chlorobenzyl)-3,4-dihydro-7-nitro-3-oxo-2H-1,4-benzoxazine monohydrochloride



- 5 Prepared from Compound 81 by method K in 46% yield, mp 79°C-shrinks,
 92-96°C-melts; MS (Cl) MH⁺482; IR (KBr) 3392, 2933, 2021, 1474, 1441,
 1146, 1118, 928, 852, 701, 528 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.95 (br s, 2H),
 7.92 (d, 1H, J = 2.5Hz), 7.87 (m, 1H), 7.42 (s, 1H), 7.36 (m, 2H), 7.24 (d, 2H, J
 = 8.8Hz), 7.16 (d, 2H, J = 8.5Hz), 6.92 (d, 2H, J = 8.5Hz), 5.30 (d, 1H, J =
 10 16.8Hz), 5.18 (m, 2H), 4.22 (m, 2H), 2.98 (t, 2H, J = 8.6Hz), 2.80 (t, 2H, J =
 8.6Hz), 2.38 (m, 1H), 2.26 (m, 1H). Anal. Calc'd for C₂₅H₂₄ClN₃O₅ · HCl ·
 H₂O: C 55.98, H 5.07, N 7.83. Found: C 55.92, H 4.80, N 7.82.

Compound 83

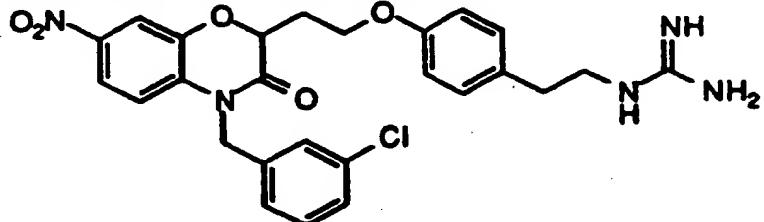
- 15** 2-[2-{4-(*N,N'*-Bis-*tert*-butoxycarbonylguanidinomethyl)phenoxy]ethyl}-4-(3-chlorobenzyl)-3,4-dihydro-7-nitro-3-oxo-2H-1,4-benzoxazine



- Prepared from intermediate 11653-35B (Reference Example 87) and N,N'-di-1-butoxycarbonyl-(4-hydroxyphenyl)methyl guanidine by method J in 65% yield, mp 67.5°C - shrinks, 84-88°C - melts. MS (FAB) MH^+ 710; IR (KBr) 3730, 3326, 3122, 3089, 2978, 2932, 2413, 1720, 1640, 1615, 1503, 1476, 1081, 931, 558 cm^{-1} ; 1H NMR ($CDCl_3$) δ 11.55 (br s, 1H), 8.59 (br s, 1H), 7.90 (d, 1H, J = 2.5Hz), 7.84 (dd, J = 2.5, 8.8Hz), 7.25 (m, 4H), 7.10 (m, 1H), 6.86 (m, 4H), 5.22 (d, 1H, J = 16.3Hz), 5.30 (d, 1H, J = 16.3Hz), 5.10 (dd, 1H, J = 3.4, 9.1Hz), 4.60 (m, 2H), 4.23 (m, 2H), 2.66 (m, 1H), 2.38 (m, 1H), 1.51 (s, 9H), 1.47 (s, 9H). Anal. Calc'd for $C_{35}H_{40}ClN_5O_9$: C 59.19, H 5.68, N 9.86. Found: C 59.10, H 6.07, N 9.74.

Compound 84

3,4-Dihydr -4-(3-chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-nitro-3-oxo-2H-1,4-benzoxazine monohydrochloride



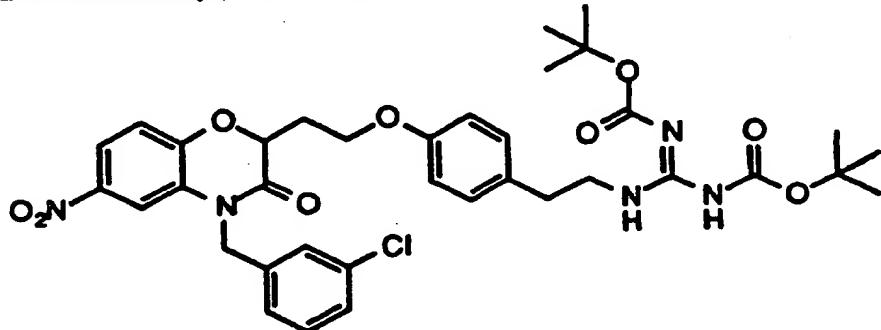
5

Prepared from Compound 83 by method K in quantitative yield, mp (dec) > 101°C; MS (FAB) MH⁺524; IR (KBr) 3326, 3156, 2968, 2878, 1695, 1665, 1599, 1513, 1473, 1441, 1389, 1178, 1148, 1022, 852, 472 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.93 (d, 0.5H, J = 2.6Hz), 7.89 (m, 1.5H), 7.62 (br t, 1H), 7.43 (s, 1H), 7.40-6.65 (v br s, 3H), 7.35 (m, 2H), 7.27 (d, 2H, J = 8.6Hz), 7.21 (d, 2H, J = 8.6Hz), 6.92 (d, 2H, J = 8.6Hz), 5.33 (d, 1H, J = 16.7Hz), 5.20 (d, m, 2H, J = 16.5Hz), 4.22 (m, 2H), 3.32 (m, 2H), 2.73 (t, 2H, J = 7.3Hz), 2.41 (m, 1H), 2.32 (m, 1H). Anal. Calc'd for C₂₆H₂₆ClN₅O₅ · HCl · H₂O: C 53.99, H 5.05, N 12.11. Found: C 54.11, H 4.95, N 12.01.

15

Compound 85

2-[2-[4-(2-(N,N-Bis-tert-butoxycarbonyl)guanidinoethyl)phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-7-nitro-2H-1,4-benzoxazine



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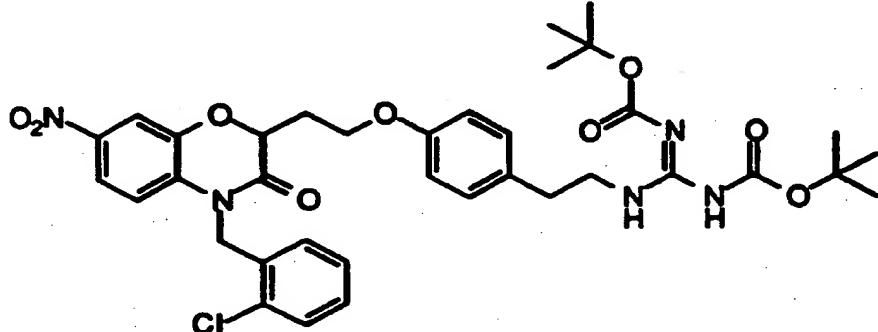
Prepared from intermediate 11653-58C (Reference Example 68) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethylguanidine in 85% yield, mp 69°C-shrinks 90-92°C-melts; MS (FAB) MH⁺724; IR (KBr) 3329, 3128, 2978, 2934, 1722, 1697, 1638, 1524, 1474, 1414, 1364, 1021, 933 cm⁻¹; ¹H NMR (CDCl₃) δ 11.47 (br s, 1H), 8.37 (br s, 1H), 7.91 (dd, 1H, J = 2.4, 8.8Hz), 7.77 (d, 1H, J = 2.5Hz), 7.27 (m, 2H), 7.19 (brs, 1H), 7.10 (m, 4H), 6.83 (d, 2H, J = 8.6Hz), 5.23 (d, 1H, J = 17.9Hz), 5.14 (d, 1H, J = 17.9Hz), 5.09 (dd, 1H, J = 4.1, 9.1Hz), 4.20 (m, 2H), 3.63 (m, 2H), 2.82 (t, 2H, J = 7.1Hz), 2.62

25

(m, 1H), 2.37 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₂ClN₅O₉: C 59.71, H 5.85, N 9.67. Found: C 59.38, H 6.04, N 9.63.

Compound 86

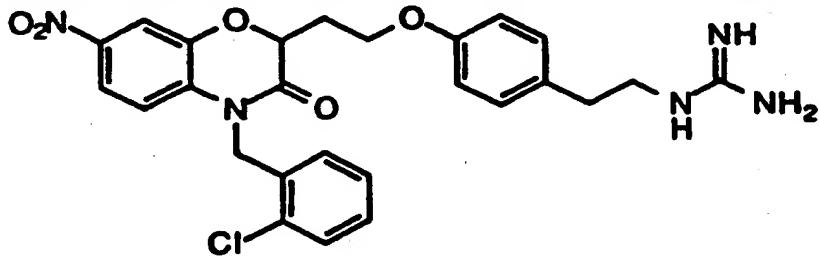
- 5 2-[2-[4-(2-(N,N'-Bis-*tert*-butoxycarbonyl)guanidino)ethyl]phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-7-nitro-3-oxo-2H-1,4-benzoxazine



Prepared from intermediate 11653-24A (Reference Example 86) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine by method L in 52% yield as a yellow foam, mp (dec) > 85°C; MS: FAB MH⁺ 724; IR (KBr) 3335, 2979, 1637, 1527, 1390, 1341, 1156, 1059 cm⁻¹; ¹H NMR (CDCl₃) δ 11.48 (br s, 1H), 7.90 (d, 1H, J = 2.50), 7.83 (dd, 1H, J = 2.52, 8.85), 7.45 (d, 1H, J = 7.90), 7.26 (m, 1H), 7.19 (m, 2H), 7.14 (d, 1H, J = 8.52), 6.94 (d, 1H, J = 7.68), 6.85 (d, 2H, J = 8.50), 6.80 (d, 1H, J = 8.90), 5.30 (d, 2H, J = 5.54), 5.08 (dd, 1H, J = 5.02), 4.23 (m, 2H), 3.65 (m, 2H), 2.82 (t, 2H, J = 7.2), 2.65 (m, 1H), 2.39 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₂ClN₅O₉: C 59.71, H 5.85, N 9.67. Found: C 59.48, H 5.89, N 9.52.

Compound 87

- 20 4-(2-Chlorobenzyl)-3,4-dihydro-2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-nitro-3-oxo-2H-1,4-benzoxazine monohydrochloride



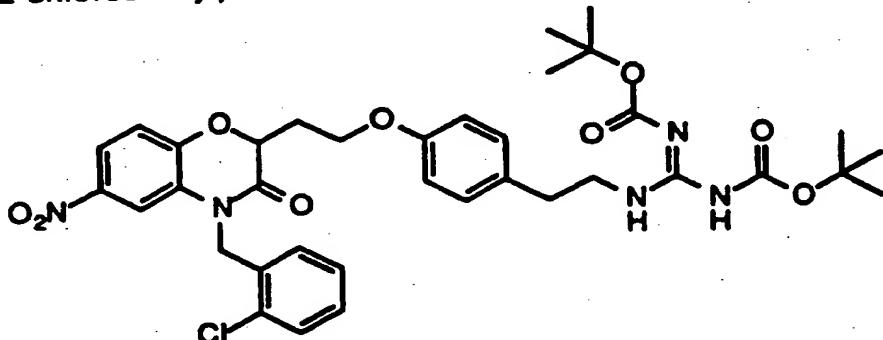
Prepared from Compound 86 by method K in 79% yield, mp 120-125°C; MS (Cl) MH⁺ 524; IR (KBr) 3368, 3322, 3168, 2932, 2878, 1694, 1502, 1334, 1234, 1028, 806 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.92 (m, 1.5H), 7.90 (d, 0.5H, J = 7.9 Hz), 7.55 (m, 2H), 7.40-6.50 (v br s., 3H), 7.34 (t, 1H, J = 7.5 Hz), 7.26 (t,

1H, *J* = 7.5 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 7.08 (m, 2H), 6.92 (d, 2H, *J* = 8.6 Hz), 5.28 (d, 1H, *J* = 17.4 Hz), 5.22 (m, 1H), 5.16 (d, 1H, *J* = 17.4 Hz), 4.22 (m, 2H), 3.34 (m, 2H), 2.71 (t, 2H, *J* = 7.6 Hz), 2.41 (m, 1H), 2.35 (m, 1H). Anal. Calc'd for $C_{26}H_{26}ClN_5O_5 \cdot HCl \cdot H_2O$: C 53.99, H 5.05, N 12.11.

5 Found C 53.75, H 5.23, N 12.09.

Compound 88

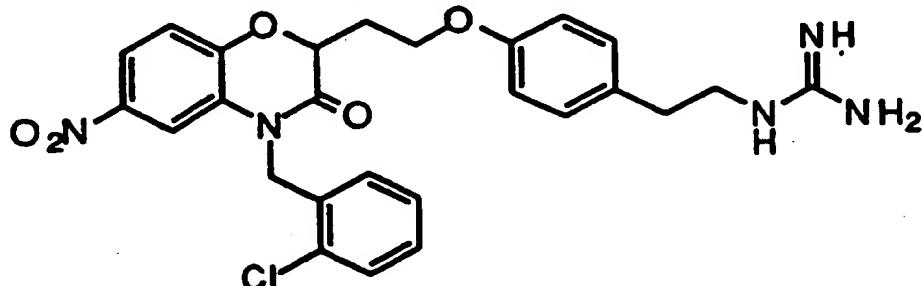
2-[2-[4-(2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl)-phenoxy]ethyl]-4-(2-chlorobenzyl)-3,4-dihydro-6-nitro-3-oxo-2H-1,4-benzoxazine



- 10 Prepared from intermediate 11653-44A (Reference Example 70) and *N,N*-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine by method L in 50% yield, mp 155°C-shrinks, 160-163°C-melts. IR (KBr) 3345, 3108, 2980, 2934, 1723, 1701, 1529, 1338, 1126, 878 cm⁻¹; ¹H NMR ($CDCl_3$) δ 11.48 (br s, 1H), 8.38 (br s, 1H), 7.91 (dd, 1H, *J* = 2.5, 8.8 Hz), 7.69 (d, 1H, *J* = 2.5 Hz), 7.46 (dd, 1H, *J* = 1.3, 9.1 Hz), 7.20 (m, 1H), 7.12 (m, 4H), 7.01 (d, 1H, *J* = 7.6 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 5.31 (s, 2H), 5.11 (dd, 1H, *J* = 4.0, 8.9 Hz), 4.22 (m, 2H), 3.63 (m, 2H), 2.82 (t, 2H, *J* = 7.2 Hz), 2.65 (m, 1H), 2.39 (m, 1H), 1.50 (s, 9H), 1.48 (s, 1H). Anal. Calc'd for $C_{36}H_{42}ClN_5O_9$: C 59.71, H 5.85, N 9.67. Found: C 59.89, H 5.84, N 9.61.

Compound 89

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-6-nitro-4-(2-chlorobenzyl)-3-oxo-2H-1,4-benzoxazine



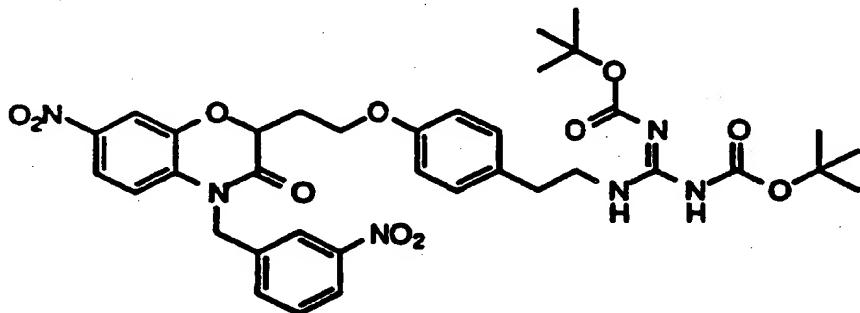
25

Prepared from Compound 88 by method K in 90% yield, mp (dec) >85 C; MS (Cl) MH⁺ 524; IR (KBr) 3335, 3156, 1651, 1524, 1515, 1446, 1343, 1269, 1243, 1108, 746 cm⁻¹; ¹H NMR (DMSO-d₆) δ 7.94 (dd, 1H, J = 2.5, 8.9 Hz), 7.64 (d, 2H, J = 2.6 Hz), 7.56 (d, 1H, J = 7.8 Hz), 7.50-6.55 (v. br. s., 3H), 5 7.30 (m, 4H), 7.19 (m, 3H), 6.90 (d, 2H, J = 8.6 Hz), 5.31 (m, 2H), 5.21 (d, 1H, J = 17.2 Hz), 4.19 (m, 2H), 3.29 (m, 2H), 2.71 (t, 2H, J = 7.7 Hz), 2.44 (m, 1H), 2.35 (m, 1H). Anal. Calc'd for C₂₆H₂₆CIN₅O₅ · HCl · 0.5 H₂O: C 54.84 H 4.96, N 12.30. Found: C 54.87, H 4.94 N 12.02.

10

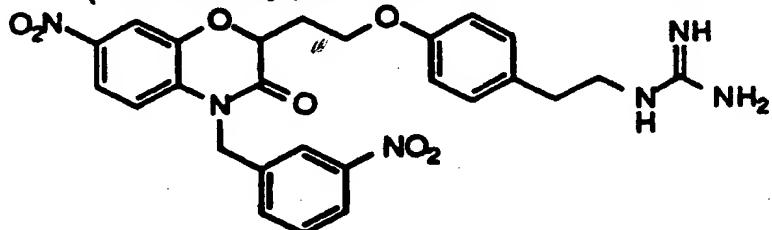
Compound 90

3,4-Dihydro-2-[2-[4-(2-(N,N'-Bis-*tert*-butoxycarbonylguanidino)ethyl)-phenoxy]ethyl]-4-(3-nitrobenzyl)-7-nitro-3-oxo-2H-1,4-benzoxazine



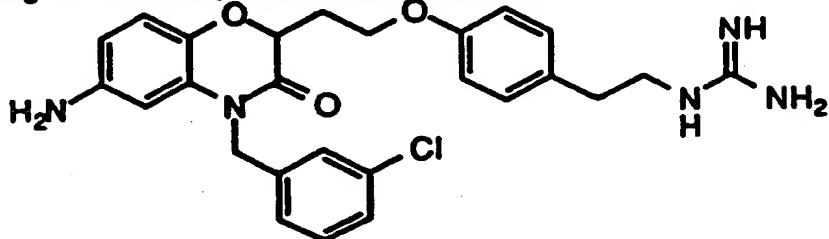
Prepared from intermediate 11653-85-B-1 (Reference Example 67) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine by method L in 41% yield, mp (dec) >84°C; MS (Cl) MH⁺ 735; IR (KBr) 3331, 2979, 2934, 1719, 1638, 1533, 1512, 1477, 1343, 1132, 812 cm⁻¹; ¹H NMR (CDCl₃) δ 11.48 (s, 1H), 8.37 (br.t., 1H), 8.16 (m, 1H), 8.12 (s, 1H), 7.91 (d, 1H, J = 2.4Hz), 7.85 (dd, 1H, J = 2.5, 8.9 Hz), 7.54 (m, 2H), 7.13 (d, 2H, J = 8.5 Hz), 20 6.89 (d, 1H, J = 8.9 Hz), 6.83 (d, 1H, J = 8.6 Hz), 5.34 (d, 1H, J = 16.6 Hz), 5.27 (d, 1H, J = 16.7 Hz), 5.10 (dd, 1H, J = 4.0, 8.9 Hz), 4.24 (m, 2H), 3.63(q, 2H, J = 7.0 Hz), 2.82 (t, 2H, J = 7.2 Hz), 2.63 (m, 1H), 2.38 (m, 1H), 1.62 (br. s., 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₂N₆O₁₁: C 58.85, H 5.76, N 11.44. Found: C 58.73, H 5.77, N 11.34.

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Compound 91**3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-nitro-
4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine**

5 Prepared from Compound 90 by method K, mp (dec) >90°C; MS (Cl) MH⁺535; IR (KBr) 3336, 3155, 1696, 1602, 1528, 1390, 1343, 1244, 1179, 927, 743 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.23 (s, 1H), 8.15 (d, 1H, *J* = 8.1 Hz), 7.89 (m, 2H), 7.72 (d, 1H, *J* = 7.7 Hz), 7.63 (t, 1H, *J* = 7.9 Hz), 7.55 (br t, 1H), 7.51-6.65 (v br s., 3H), 7.31 (d, 1H, *J* = 7.31 Hz), 7.20 (d, 2H, *J* = 8.6 Hz), 6.91 (d, 2H, *J* = 8.6 Hz), 5.43 (d, 1H, *J* = 16.6 Hz), 5.34 (d, 1H, *J* = 17.3 Hz), 5.23 (dd, 1H, *J* = 4.1, 8.7 Hz), 4.21 (m, 2H), 3.30 (m, 2H), 2.71 (t, 2H, *J* = 7.3 Hz), 2.41 (m, 1H), 2.30 (m, 1H). Anal. Calc'd for C₂₆H₂₆N₆O₇ · HCl · 0.7 H₂O: C 53.51, H 4.91, N 14.40. Found: C 53.87, H 4.77, N 14.72.

15

Compound 92**6-Amino-4-(3-chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-1,4-benzoxazine**

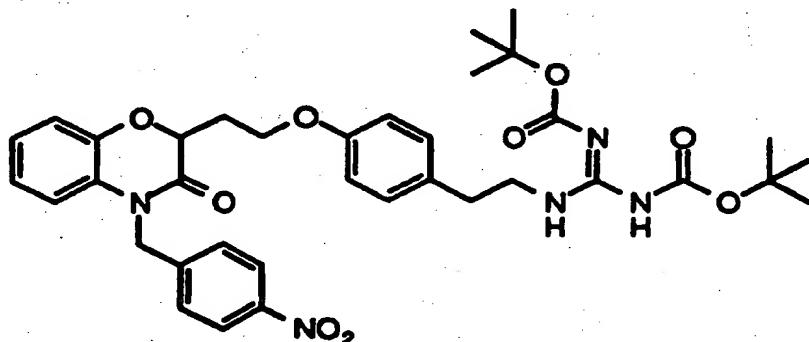
20 4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-6-nitro-3-oxo-2H-1,4-benzoxazine (0.3 g) was warmed in ethanol (5 ml) and H₂O (4 ml) until completely in solution. Iron powder (0.19 g, 6.8 eq) was stirred in followed by NH₄Cl (0.02 g, 0.7 eq) and the reaction continued at reflux for 5 hours. While still hot, the mixture was filtered through celite and the yellow filtrate concentrated down to a yellow oil. After drying in vacuo at 80 °C, the product was collected as a yellow solid in 85% yield, mp (dec) >94°C; MS (Cl) MH⁺494; IR (KBr) 3332, 1667, 1614, 1512, 1467, 1396, 1243, 830, 774, 680 cm⁻¹; ¹H NMR (DMSO-*d*₆/CDCl₃) δ 7.66 (br s, 1H), 7.58-6.50 (v br s, 3H), 7.36 (m, 4H), 7.20 (m, 3H), 6.91 (d, 2H, *J* = 8.6 Hz).

6.74 (d, 1H, $J = 8.4$ Hz), 6.26 (d, 1H, $J = 2.2$ Hz), 6.21 (dd, 1H, $J = 2.2, 8.4$ Hz), 5.08 (d, 1H, $J = 16.7$ Hz), 4.99 (d, 1H, $J = 16.5$ Hz), 5.12-4.78 (v-br s., 1H), 4.79 (dd, 1H, $J = 4.0, 8.9$ Hz), 4.15 (m, 2H), 3.33 (m, 2H), 2.71 (t, 2H, $J = 7.5$ Hz), 2.30 (m, 1H), 2.18 (m, 1H). Anal. Calc'd for $C_{26}H_{28}ClN_5O_3 \cdot HCl \cdot 0.5$

5 H₂O: C 57.89, H 5.61, N 12.98. Found: C 57.64, H 5.48, N 12.63.

Compound 93

2-[2-[4-(2-(*N,N'*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(4-nitrobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



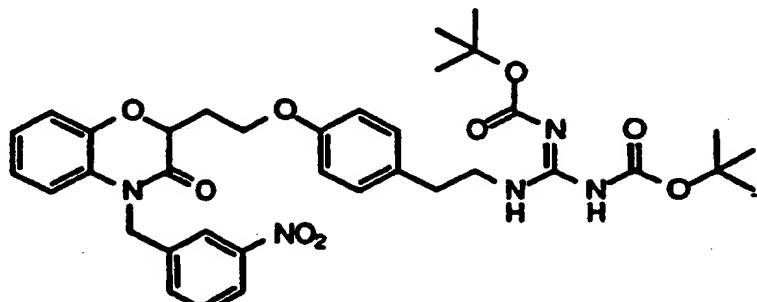
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Prepared from intermediate 11653-173 (Reference Example 71) and *N,N'*-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine by method L in 61% yield, mp (dec) $>78^\circ\text{C}$; IR (KBr) 3331, 2977, 1722, 1689, 1638, 1513, 1500, 1467, 1278, 922, 859 cm⁻¹; ¹H NMR (CDCl_3) δ 11.48 (br s., 1H), 8.37 (br t, 1H), 8.19 (d, 2H, $J = 8.8$ Hz), 7.41 (d, 2H, $J = 8.8$ Hz), 7.13 (d, 2H, $J = 8.6$ Hz), 7.03 (m, 2H), 6.92 (m, 1H), 6.85 (d, 2H, $J = 8.6$ Hz), 6.75 (d, 1H, $J = 7.9$ Hz), 5.29 (d, 1H, $J = 16.7$ Hz), 5.18 (d, 1H, $J = 16.7$ Hz), 4.95 (dd, 1H, $J = 3.9, 9.3$ Hz), 4.22 (m, 2H), 3.64 (m, 2H), 2.81 (t, 2H, $J = 7.3$ Hz), 2.58 (m, 1H), 2.35 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for $C_{36}H_{43}N_5O_9 \cdot 0.5$

15 H₂O: C 61.88, H 6.35, N 10.02. Found: C 62.07, H 6.32, N 9.85.

Compound 94

2-[2-[4-(2-(*N,N'*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine



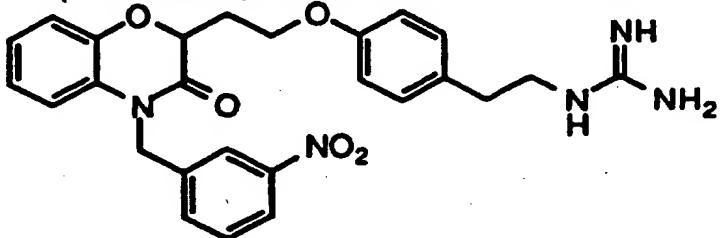
25

Prepared from intermediate 11653-180 (Reference Example 61) and N,N'-di-t-butoxycarbonyl-2-(4-hydroxyph nyl)ethyl-guanidine by method L in 64% yield, mp (dec) >144°C; MS (FAB) MH⁺ 690; IR (KBr) 3333, 2979, 1769, 1720, 1684, 1641, 1613, 1582, 1526, 1512, 1501, 1467, 1403, 1303, 1279, 1208, 1020 cm⁻¹; ¹H NMR (CDCl₃) δ 11.50 (br s, 1H), 8.37 (br t, 1H), 8.15 (s, 1H), 8.13 (s, 1H), 7.58 (d, 1H, J = 7.7Hz), 7.54 (m, 1H), 7.12 (d, 2H, J = 8.6Hz), 7.02 (m, 2H), 6.91 (m, 2H), 6.85 (d, 1H, J = 8.6Hz), 6.79 (d, 1H, J = 7.7Hz), 5.25 (s, 2H), 4.98 (dd, 1H, J = 3.9, 9.4Hz), 4.22 (m, 2H), 3.63 (m, 2H), 2.81 (t, 2H, J = 7.3Hz), 2.58 (m, 1H), 2.34 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H).

5 10 Anal. Calc'd for C₃₆H₄₃N₅O₉ · H₂O: C 61.09, H 6.41, N 9.89. Found: C 61.40, H 6.47, N 9.55.

Compound 95

3,4-Dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-
15 4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

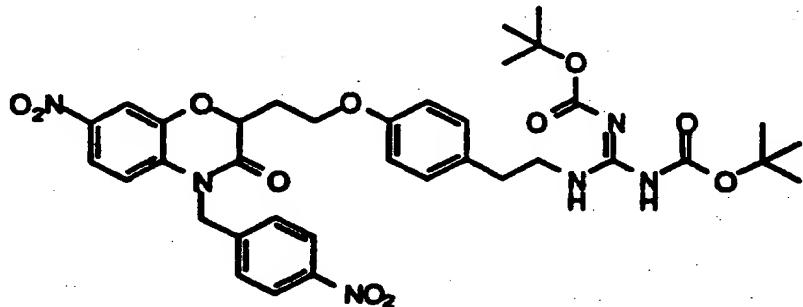


Prepared from Compound 94 by method K in 58% yield, mp (dec) >79°C; MS (FAB) MH⁺ 490; IR (KBr) 3321, 3146, 1665, 1529, 1500, 1466, 1399, 1349, 1322, 1279, 1249, 1154, 1097, 1063, 1022, 924, 810, 687, 468 cm⁻¹.

20 ¹H NMR (DMSO-d₆) δ 8.18 (s, 1H), 8.13 (d, 1H, J = 7.9 Hz), 7.68 (m, 1H), 7.60-6.40 (v br s, 3H), 7.39 (s, 1H), 7.20 (m, 2H), 7.08 (m, 3H), 6.98 (m, 3H), 6.92 (d, 1H, J = 8.4 Hz), 5.36 (d, 1H, J = 18.7 Hz), 5.28 (d, 1H, J = 17.0 Hz), 5.02 (m, 1H), 4.28 (t, 1H, J = 6.6 Hz), 4.18 (m, 1H), 3.35 (m, 3H), 2.72 (t, 2H, J = 6.3 Hz), 2.40 (m, 1H), 2.27 (m, 1H). Anal. Calc'd for C₂₆H₂₇N₅O₅ · 2.1 HCl: C 55.16, H 5.18, N 12.37. Found: C 55.08, H 5.23, N 12.21.

Compound 96

2-[2-[4-(2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-7-nitro-4-(4-nitrobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

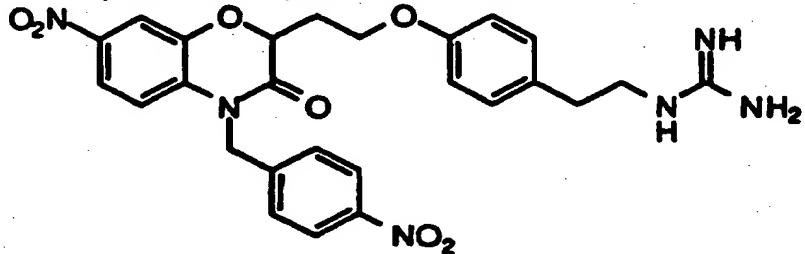


- 5 Prepared from 12279-11 (Reference Example 62) by method L in 43% yield and isolated as a yellow solid, mp (dec) >77°C; MS (FAB) MH⁺ 735; IR (KBr) 3329, 3087, 2976, 2932, 2871, 1720, 1639, 1610, 1474, 1390, 1155, 1022, 882, 577, 461 cm⁻¹; ¹H NMR (CDCl₃) δ 11.49 (br s, 1H), 8.37 (br t, 1H), 8.21 (d, 2H, J = 8.7Hz), 7.91 (d, 1H, J = 2.5Hz), 7.84 (dd, 1H, J = 2.5, 8.9), 7.40 (d, 2H, J = 8.6Hz), 7.14 (d, 2H, J = 8.6Hz), 6.83 (dd, 3H, J = 2.5, 9.0Hz), 5.35 (d, 1H, J = 15.4Hz), 5.25 (d, 1H, J = 15.4Hz), 5.08 (dd, 1H, J = 4.0, 8.9Hz), 4.22 (m, 2H), 3.63 (m, 2H), 2.82 (t, 2H, J = 7.4Hz), 2.63 (m, 1H), 2.38 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₂N₆O₁₁ · C₃H₆O: C 59.03, H 6.10, N 10.60. Found: C 58.96, H 6.17, N 10.54.
- 10

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Compound 97

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-nitro-4-(4-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

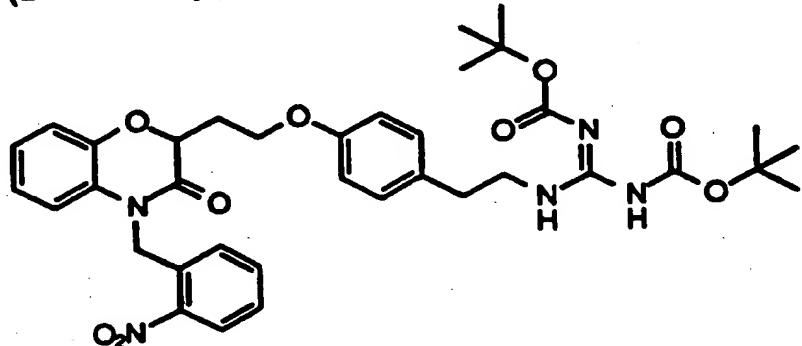


- 20 Prepared from Compound 96 by method K in quantitative yield, mp (dec) >141°C; MS (FAB) MH⁺ 535; IR (KBr) 3323, 3158, 2948, 1702, 1667, 1598, 1470, 1434, 1396, 1182, 1144, 1107, 1012, 995, 898, 860, 826 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 8.22 (d, 2H, J = 8.8 Hz), 7.92 (s, 1H), 7.89 (d, 1H, J = 2.6 Hz), 7.61 (m, 3H), 7.60-6.65 (v br s, 2H), 7.23 (m, 4H), 6.94 (d, 2H, J = 8.6 Hz), 5.47 (d, 1H, J = 17.3 Hz), 5.36 (d, 1H, J = 17.3 Hz), 5.27 (dd, 1H, J = 8.8, 4.2 Hz), 4.23 (m, 2H), 3.35 (m, 2H), 2.74 (t, 2H, J = 7.4 Hz), 2.45 (m, 1H), 2.38
- 25

(m, 1H). Anal. Calc'd for C₂₆H₂₆N₆O₇ · HCl · 0.9 H₂O · 0.2 IPA: C 53.32, H 5.11, N 14.02. Found: C 53.07, H 4.84, N 13.74.

Compound 98

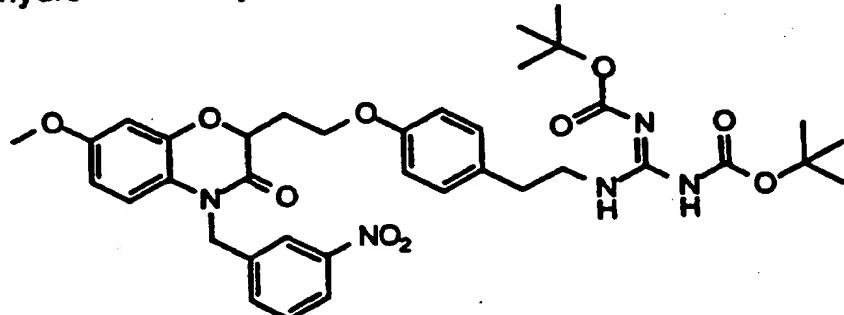
- 5 2-[2-[4-(2-(N,N'-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(2-nitrobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- Prepared by method L using intermediate 11653-174-A (Reference Example 73) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine in 10 40% yield as a yellow solid, mp (dec) >65°C; MS (Cl) MH⁺ 690; IR (KBr) 3330, 3151, 2978, 2934, 1723, 1694, 1616, 1528, 1502, 1302, 1277, 1228, 1087, 1022, 933, 880, 562, 464 cm⁻¹; ¹H NMR (CDCl₃) δ 11.40 (br s, 1H), 8.36 (br s, 1H), 8.18 (d, 1H, J = 8.12Hz), 7.42 (m, 2H), 7.10 (m, 2H), 6.96 (m, 4H), 6.85 (m, 1H), 6.73 (d, 2H, J = 8.27Hz), 5.50 (d, 2H, J = 17.95Hz), 4.95 (dd, 1H, J = 9.59, 4.21Hz), 4.16 (m, 2H), 3.56 (m, 2H), 2.77 (m, 2H), 2.57 (m, 1H), 2.35 (m, 1H), 1.46 (s, 9H), 1.45 (s, 9H). Anal. Calc'd for C₃₆H₄₃N₅O₉ · 0.9 H₂O: C 61.25, H 6.40, N 9.92. Found: C 60.79, H 6.76, N 10.39.

Compound 99

- 20 2-[2-[4-(2-(N,N'-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-7-methoxy-4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine



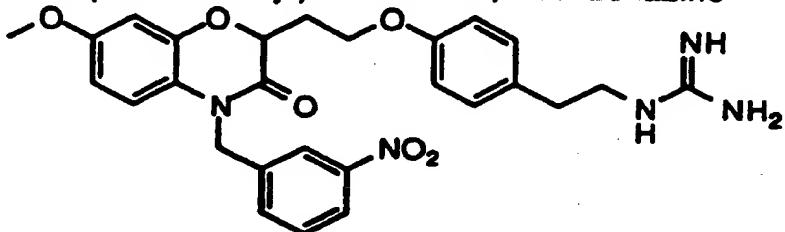
- Prepared by method L using intermediate 12279-18-A (Reference Example 63) and N,N'-di-*t*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine in 25 83% yield, mp (dec) >71°C; MS (FAB) MH⁺ 720; IR (KBr) 3329, 2977, 2934,

1722, 1683, 1639, 1532, 1413, 1350, 1330, 1247, 1164, 1057, 916, 729,
~~529 cm⁻¹~~; ¹H NMR (CDCl₃) δ 11.48 (s, 1H), 8.37 (br s, 1H), 8.15 (s, 1H),
8.12 (s, 1H), 7.53 (m, 2H), 7.13 (d, 2H, J = 8.62Hz), 6.86 (d, 2H, J = 8.62Hz),
6.68 (d, 1H, J = 8.88Hz), 6.61 (d, 1H, J = 2.72Hz), 6.47 (dd, 1H, J = 8.85,
5 2.70Hz), 5.21 (s, 2H), 4.96 (dd, 1H, J = 9.36, 3.95Hz), 4.23 (m, 2H), 3.74 (s,
3H), 3.63 (m, 2H), 2.81 (t, 2H, J = 7.22Hz), 2.57 (m, 1H), 2.33 (m, 1H), 1.50
(s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₇H₄₅N₅O₁₀: C 61.74, H 6.30, N 9.73.
Found: C 61.24, H 6.43, N 9.76.

10

Compound 100

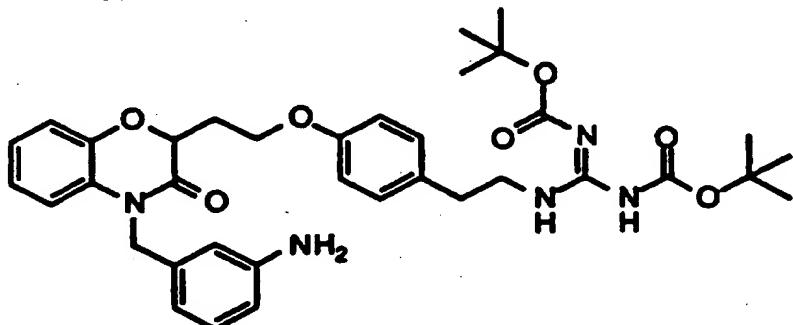
3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-methoxy-
4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine



Prepared from Compound 99 by method K in 87% yield, mp (dec) > 68°C;
15 MS (Cl) MH⁺520; IR (KBr) 3317, 3147, 2930, 1466, 1407, 1357, 1324,
1309, 1163, 1135, 922, 798, 669, 530 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.16 (s,
1H), 8.13 (d, 1H, J = 8.28Hz), 7.66 (m, 2H), 7.60 (t, 2H, J = 7.30Hz), 7.53-
6.70(v br s, 2H), 7.20 (d, 2H, J = 8.48Hz), 7.01 (d, 1H, J = 8.92Hz), 6.92 (d,
2H, J = 8.48Hz), 6.69 (d, 1H, J = 2.79Hz), 6.55 (dd, 1H, J = 2.70, 8.88Hz),
20 5.28 (d, 2H, J = 2.72Hz), 4.98 (dd, 1H, J = 4.05, 8.81Hz), 4.20 (m, 2H), 3.68
(s, 3H), 3.32 (m, 2H), 2.71 (t, 2H, J = 7.16Hz) 2.37 (m, 1H), 2.23 (m, 1H). Anal.
Calc'd for C₂₇H₂₉N₅O₆ · HCl · 0.5 H₂O: C 57.39, H 5.53, N 12.39. Found: C
57.71, H 5.90, N 11.99.

Compound 101

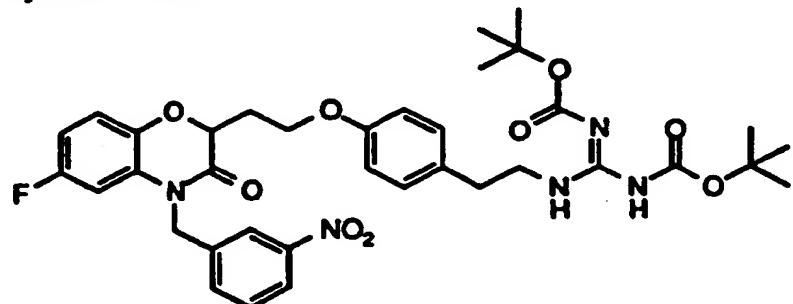
4-(3-Aminobenzyl)-2-[2-{4-(2-(N,N'-bis-*t*-butoxycarbonylguanidino)ethyl}phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- 5 Prepared by method L using intermediate 12279-13-A (Reference Example 65) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine, and isolated by flash chromatography, eluting with acetone/hexane in 55% yield as a white solid, mp (dec) >68°C; MS (FAB) MH⁺660; IR (KBr) 3335, 2977, 1722, 1685, 1638, 1512, 1500, 1466, 1408, 1366, 1329, 1244, 1155, 1131,
- 10 1057, 809, 749, 688 cm⁻¹; ¹H NMR (CDCl₃) δ 11.48 (s, 1H), 8.37 (br t, 1H), 7.12 (m, 3H), 6.95 (m, 2H), 6.87 (m, 4H), 6.85 (d, 1H, J = 8.48Hz), 6.64 (d, 1H, J = 7.54Hz), 6.56 (d, 1H, J = 11.1Hz), 5.07 (dd, 2H, J = 15.97, 24.50Hz), 4.93 (dd, 1H, J = 3.83, 5.49Hz), 4.23 (m, 2H), 3.62 (m, 4H), 2.81 (t, 2H, J = 7.16Hz), 2.56 (m, 1H), 2.33 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₅N₅O₇: C 65.54, H 6.87 N 10.61. Found: C 65.43, H 6.92, N 10.38.

Compound 102

2-[2-{4-(2-(N,N'-Bis-*t*-butoxycarbonylguanidino)ethyl}phenoxy]ethyl]-3,4-dihydro-6-fluoro-4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine

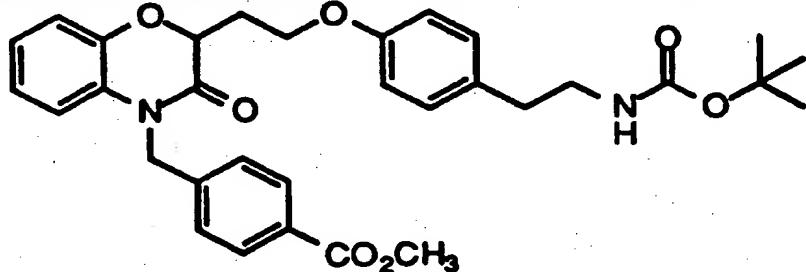


- Prepared by method L using intermediate 12279-21 (Reference Example 64) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine in 77% yield, mp (dec) >69°C; MS (FAB) MH⁺708; IR (KBr) 3330, 2978, 1696, 1638, 1533, 1507, 1453, 1415, 1350, 1249, 1155, 948, 670 cm⁻¹; ¹H NMR

(CDCl₃) δ 11.47 (br s, 1H), 8.37 (br t, 1H), 8.16 (d, 1H, J = 7.1 Hz), 8.11 (br s, 1H), 7.53 (m, 2H), 7.14 (d, 2H, J = 8.6 Hz), 6.98 (dd, 1H, J = 5.1, 8.9 Hz), 6.85 (d, 2H, J = 8.6 Hz), 6.70 (m, 1H), 6.51 (dd, 1H, J = 2.8, 9.4 Hz), 5.21 (d, 1H, J = 16.4 Hz), 5.20 (d, 1H, J = 16.4 Hz), 4.95 (dd, 1H, J = 4.0, 9.3 Hz), 4.22 (m, 2H), 3.64 (m, 2H), 2.81 (t, 2H, J = 7.1 Hz), 2.63 (m, 1H), 2.34 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for C₃₆H₄₂FN₅O₉ · 1.5 H₂O: C 60.41, H 6.34, N 9.78. Found: C 60.36, H 6.17, N 10.06.

Compound 103

10 2-[2-{2-[2-(t-Butoxycarbonylamino)ethyl]phenoxy}ethyl]-
4-(4-carbomethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

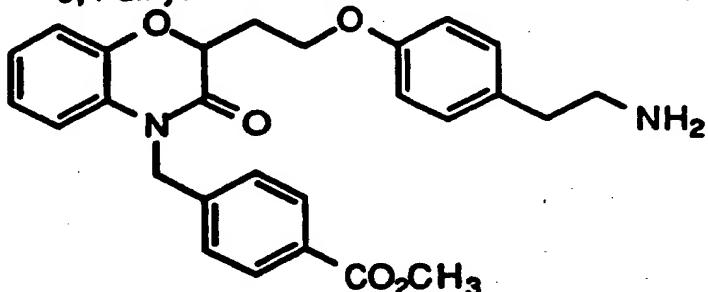


Prepared from intermediate 11758-71-2 (Reference Example 81) and 4-[2-(N-t-butoxycarbonylamino)-ethyl]phenol by method L to afford product as a
 15 white solid in 69% yield, mp 110-112°C; ¹H NMR (CDCl₃) δ 8.00 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.98-7.04 (m, 2H), 6.89-6.95 (m, 3H), 6.78 (dd, J = 1.3, 8.5 Hz, 1H), 5.21 (br s, 2H), 4.96 (dd, J = 4.0, 9.5 Hz, 1H), 4.54 (br s with shoulders, 1H), 4.15-4.30 (m, 2H), 3.90 (s, 3H), 3.31-3.36 (m, 2H), 2.74 (t, J = 6.7 Hz, 2H), 2.53-2.63 (m, 1H), 2.33 (ddt, J = 14.1, 9.5, 4.8 Hz, 1H), 1.44 (s, 9H). ¹³C NMR (CDCl₃) δ 166.7, 166.4, 157.3, 155.9, 144.2, 141.3, 131.3, 130.2 (CH), 129.8 (CH), 129.5, 128.7, 126.5 (CH), 124.3 (CH), 122.9 (CH), 117.5 (CH), 115.3 (CH), 114.7 (CH), 76.6, 73.9 (CH), 63.1 (CH₂), 52.1 (CH₃), 45.2 (CH₂), 41.9 (CH₂), 35.3 (CH₂), 30.4 (CH₂), 28.4 (CH₃). IR 3376, 1713, 1684 cm⁻¹. MS (FAB) 561 (MH⁺), 461, 324 (base). Anal. Calc'd. for C₃₂H₃₆N₂O₇: C, 68.56; H, 6.47; N, 5.00.
 20 Found: C, 68.16; H, 6.45; N, 4.90.

Compound 104

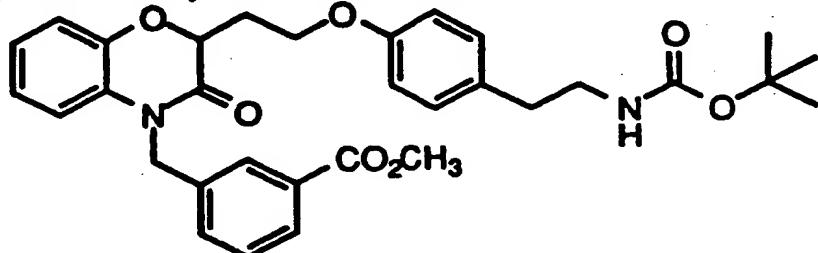
2-[2-{4-(2-Aminoethyl)phenoxy}ethyl]-4-(4-carbomethoxybenzyl)-

3,4-dihydro-3-oxo-2H-1,4-benzoxazine



- 5 Prepared from Compound 103 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl. The resulting solid was triturated with ether to afford product as a white powder (182 mg; 88% yield; mp=164-165 °C). ¹H NMR (DMSO-*d*₆) δ 8.40 (br s, 3H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.77-7.01 (m, 6H), 5.21 (s, 2H), 4.94 (dd, *J* = 4.0, 9.3 Hz, 1H), 4.19-4.27 (m, 2H), 3.90 (s, 3H), 3.06-3.12 (m, 2H), 2.90-2.96 (m, 2H), 2.51-2.60 (m, 1H), 2.29-2.37 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 165.9, 165.6, 157.0, 143.4, 140.7, 129.5 (CH), 129.2 (CH), 128.8, 128.5, 127.9, 125.8 (CH), 123.7 (CH), 122.3 (CH), 116.8 (CH), 114.7 (CH), 114.2 (CH), 73.1 (CH), 62.5 (CH₂), 51.5 (CH₃), 44.4 (CH₂), 40.4 (CH₂), 32.2 (CH₂), 29.6 (CH₂). IR 2700-3200 (br), 1722, 1705, 1680 cm⁻¹. MS 461 (MH⁺). Anal. Calc'd. for C₂₇H₂₈N₂O₅/C₂H₃O₂: C, 60.62; H, 5.09; N, 4.88. Found: C, 60.31; H, 5.07; N, 4.78.

Compound 105

20 2-[2-{4-[2-(t-Butoxycarbonylamino)ethyl]phenoxy}ethyl]-
4-(3-carbomethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

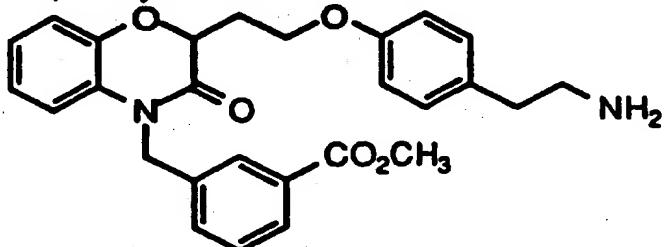
- Prepared from intermediate 11758-93-2A (Reference Example 82) and 4-[2-(N-t-butoxycarbonylamino)ethyl]phenol, by method L and isolated as a white solid, 66.2% yield, mp 112-113°C; ¹H NMR (CDCl₃) δ 7.93-7.95 (m, 2H), 7.38-7.41 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.88-7.02 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.81 (dd, *J* = 1.5, 7.7 Hz, 1H), 5.20 (s, 2H), 4.96 (dd, *J* = 4.0, 9.4 Hz,

1H), 4.51 (br s, 1H), 4.18-4.26 (m, 2H), 3.90 (s, 3H), 3.32-3.35 (br m, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.55-2.60 (m, 1H), 2.32-2.38 (m, 1H), 1.43 (s, 9H). IR 3370, 1724, 1688 cm⁻¹. MS (FAB) 561 (MH⁺), 324. Anal. Calc'd. for C₃₂H₃₆N₂O₇: C, 68.56; H, 6.47; N, 5.00. Found: C, 68.37; H, 6.63; N, 4.88.

5

Compound 106

2-[2-[4-(2-Aminoethyl)phenoxy]ethyl]-4-(3-carbomethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

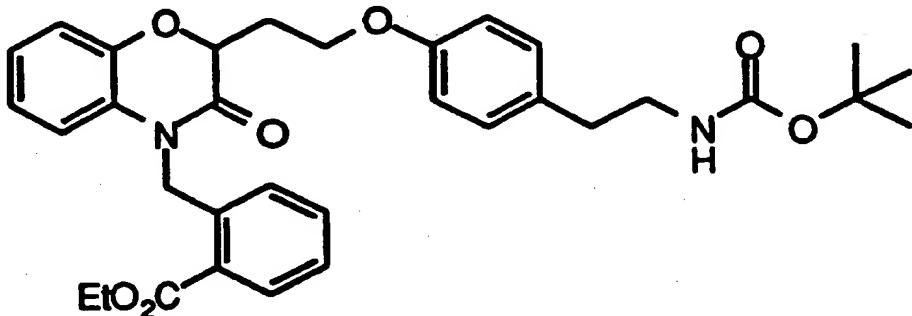


- 10 Prepared from Compound 105 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated as a cream-colored solid, 92% yield, mp=112-114.5°C; ¹H NMR (DMSO-d₆) δ 7.90 (br s, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.77 (br s, 3H), 7.47-7.54 (m, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.00-7.08 (m, 4H), 6.95 (d, J = 8.5 Hz, 2H), 5.26 (s, 2H), 5.00 (dd, J = 4.0, 8.9 Hz, 1H), 4.19-4.23 (m, 2H), 3.84 (s, 3H), 3.02 (t, J = 7.8 Hz, 2H), 2.79 (t, J = 7.8 Hz, 2H), 2.35-2.40 (m, 1H), 2.23-2.28 (m, 1H). IR 2900-3100 (br), 1717, 1683 cm⁻¹. MS 461 (MH⁺). Anal. Calc'd. for C₂₇H₂₈N₂O₅/C₂HF₃O₂: C, 60.62; H, 5.09; N, 4.88. Found: C, 60.27; H, 5.31; N, 4.68.
- 15

20

Compound 107

2-[2-[4-[2-(t-Butoxycarbonylamino)ethyl]phenoxy]ethyl]-4-(2-carboethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

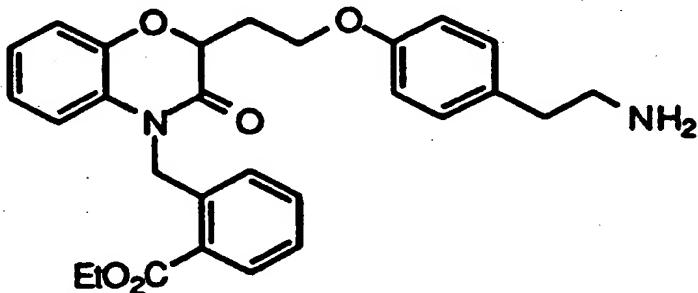


- Prepared from intermediat 11758-82-2 (Reference-Example 83) and 4-[2-(N-t-butoxycarbonylamino)-ethyl]ph nol, by m thod L and isolat d as a white solid in 76.9% yield, mp 103-105 C; ¹H NMR (CDCl₃) δ 8.07 (dd, J =
- 25

1.5, 7.6 Hz, 1H), 7.41 (dt, J = 1.5, 7.6 Hz, 1H), 7.32 (dt, J = 0.9, 7.6 Hz, 1H),
 7.10 (d, J = 8.6 Hz, 2H), 6.95-7.07 (m, 3H), 6.85-6.92 (m, 3H with a 2H
 doublet (J = 8.6 Hz) at δ 6.87), 6.72 (dd, J = 1.4, 8.0 Hz, 1H), 5.63 (d, J = 17.9
 Hz, 1H), 5.54 (d, J = 17.9 Hz, 1H), 4.97 (dd, J = 3.9, 9.4 Hz, 1H), 4.52 (br s,
 5 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.20-4.28 (m, 2H), 3.32-3.36 (br m, 2H), 2.74 (t,
 J = 6.8 Hz, 2H), 2.56-2.69 (m, 1H), 2.36 (ddt, J = 14.4, 9.3, 4.8 Hz, 1H), 1.43
 (t, J = 7.1 Hz, 3H), 1.42 (s, 9H). ^{13}C NMR δ 166.9, 166.4, 157.4, 155.9,
 144.2, 137.7, 132.8 (CH), 131.5 (CH), 131.3, 129.8 (CH), 129.0, 128.5, 127.1
 (CH), 125.6 (CH), 124.1 (CH), 122.9 (CH), 117.3 (CH), 115.6 (CH), 114.7
 (CH), 73.7 (CH), 63.3 (CH₂), 61.2 (CH₂), 50.9, 44.5 (CH₂), 41.9 (CH₂), 35.3
 (CH₂), 30.4 (CH₂), 28.4 (CH₃), 14.4 (CH₃).

Compound 108

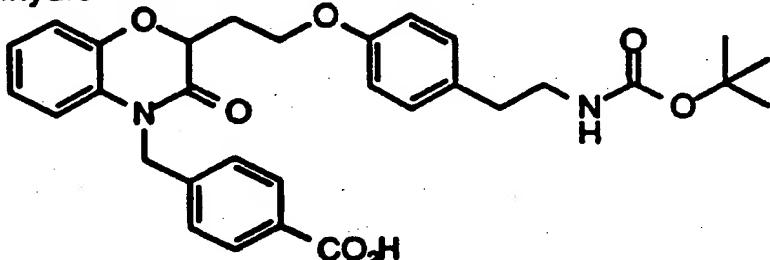
2-[2-[4-(2-Aminoethyl)phenoxy]ethyl]-4-(2-carboethoxybenzyl)-
 15 3,4-dihydro-3-oxo-2H-1,4-benzoxazine



Prepared from Compound 107 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated as a white powder in 94.5% yield, mp 107.5-109°C; ^1H NMR (DMSO- d_6) δ 7.99 (dd, J = 1.5, 6.2
 20 Hz, 1H), 7.75 (br s, 3H), 7.39-7.53 (m, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.02-7.10
 (m, 3H), 6.92-6.99 (m, 3H with a 2H doublet at δ 6.94), 6.81 (d, J = 8.0 Hz,
 1H), 5.51 (d, J = 17.5 Hz, 1H), 5.39 (d, J = 17.5 Hz, 1H), 5.04 (dd, J = 4.1, 8.7
 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.18-4.23 (m, 2H), 2.90-3.02 (m, 2H), 2.75-
 2.81 (m, 2H), 2.28-2.45 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H). IR 2975-3100
 25 (br), 1690 (sh), 1680 cm⁻¹. MS 475 (MH⁺). Anal. Calc'd. for
 $C_{28}H_{30}N_2O_5/1.0C_2HF_3O_2/1.5H_2O$: C, 58.53; H, 5.57; N, 4.55. Found: C,
 58.48; H, 5.44; N, 4.55.

Compound 109

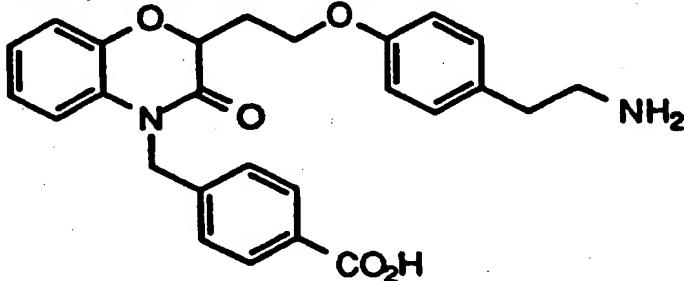
4-[2-[2-(4-(t-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-
3,4-dihydro-3-oxo-2H-1,4-benzoxazin-4-yl)methylbenzoic acid



- 5 **Method O:** Compound 103 (150 mg, 1 eq) and 1N NaOH (2.5 eq) in methanol (10 mL) were heated in an oil bath at 50°C for 26 h. After evaporation of the methanol, the residue was diluted with water (20 mL), cooled to 0 °C, and acidified with 1N citric acid (1mL). The precipitate was collected, washed with water and dried to give product as a white solid in
 10 89% yield, mp=147-148°C; ^1H NMR (DMSO- d_6) δ 8.04 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.75-7.04 (m, 6H), 5.22 (br s, 2H), 4.96 (dd, J = 3.8, 9.0 Hz, 1H), 4.55 (br s, 1H), 4.10-4.28 (m, 2H), 3.31-3.36 (m, 2H), 2.73 (t, J = 6.3 Hz, 2H), 2.55-2.61 (m, 1H), 2.34 (ddt, J = 14.1, 9.8, 5.1 Hz, 1H), 1.43 (s, 9H). IR 3300-3350 (br), 1688 (br) cm $^{-1}$. MS (FAB) 547 (MH^+), 447 (M-Boc) $^+$, 310 (base). Anal. Calc'd. for C₃₁H₃₄N₂O₇: C, 68.12; H, 6.27; N, 5.12. Found: C, 67.71; H, 6.47; N, 5.00.

Compound 110

4-[3,4-Dihydro-2-[2-(4-(2-aminoethyl)phenoxy)]ethyl-3-oxo-
2H-1,4-benzoxazin-4-yl)methylbenzoic acid

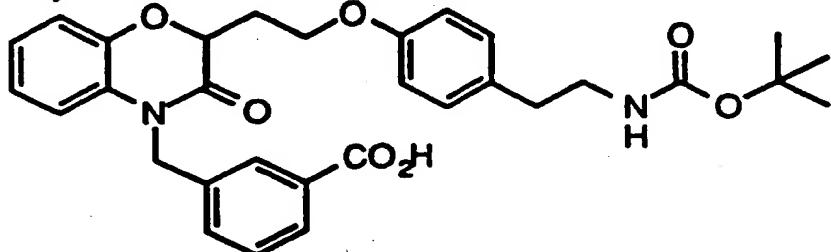


- 20 Prepared from Compound 109 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated a white powder in 98% yield, mp195-197°C; ^1H NMR (DMSO- d_6) δ 12.97 (br s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.77 (br s, 3H), 7.38 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.97-7.05 (m, 4H), 6.95 (d, J = 8.3 Hz, 2H), 5.28 (d, J = 16.3 Hz, 1H), 5.20 (d, J = 16.3 Hz, 1H), 5.00 (dd, J = 4.0, 8.7 Hz, 1H), 4.18-4.22 (m, 2H), 2.98-3.02

(m, 2H), 2.78 (t, $J = 7.8$ Hz, 2H), 2.35-2.40 (m, 1H), 2.23-2.28 (m, 1H). ^{13}C NMR δ 166.9, 165.8, 157.2, 143.6, 141.6, 129.8 (CH), 129.7 (CH), 129.3, 128.3, 126.6 (CH), 123.9 (CH), 122.8 (CH), 117.0 (CH), 115.7 (CH), 114.7 (CH), 73.0 (CH), 63.1 (CH₂), 43.7 (CH₂), 39.9 (CH₂), 31.9 (CH₂), 29.4 (CH₂).
5 IR 3000-3200 (br), 1681, 1503 cm⁻¹. MS 447 (MH⁺), 429 (M-OH)⁺. Anal. Calc'd. for C₂₆H₂₆N₂O₅/C₂HF₃O₂/ 0.5H₂O: C, 59.05; H, 4.96; N, 4.92. Found: C, 58.96; H, 4.71; N, 4.76.

Compound 111

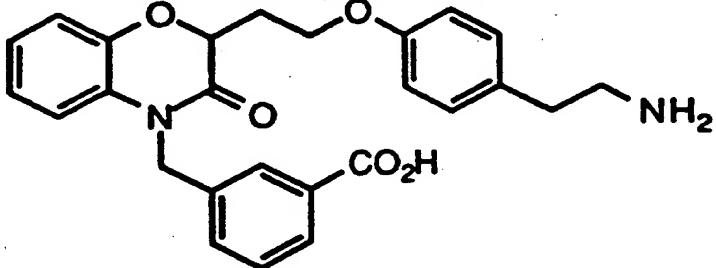
10 3-{3,4-Dihydro-2-[2-(4-(2-(1-butoxycarbonylamino)ethyl)phenoxy)]ethyl-3-oxo-2H-1,4-benzoxazin-4-yl)methylbenzoic acid



Prepared from Compound 105 by method O and isolated as a white glass in 92% yield, mp 76-78°C; ^1H NMR (DMSO-*d*₆) δ 7.87 (br s, 1H), 7.82 (d, $J = 7.3$ Hz, 1H), 7.51 (d, $J = 8.8$ Hz, 1H), 7.47 (q, $J = 7.4$ Hz, 1H), 7.10 (d, $J = 8.5$ Hz, 2H), 6.97-7.07 (m, 4H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.85 (br s, 1H), 5.24 (s, 2H), 4.98 (dd, $J = 4.1, 8.8$ Hz, 1H), 4.15-4.19 (m, 2H), 3.06-3.10 (br q, $J = 7.6$ Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 2.32-2.37 (m, 1H), 2.20-2.25 (m, 1H), 1.36 (s, 9H). IR 2800-3100 (br), 1704, 1700 (sh) cm⁻¹. MS 547 (MH⁺), 473 (base).
15 Anal. Calc'd. for C₃₁H₃₄N₂O₇/0.5 H₂O: C, 67.01; H, 6.35; N, 5.04. Found:
20 C, 67.03; H, 6.44; N, 4.95.

Compound 112

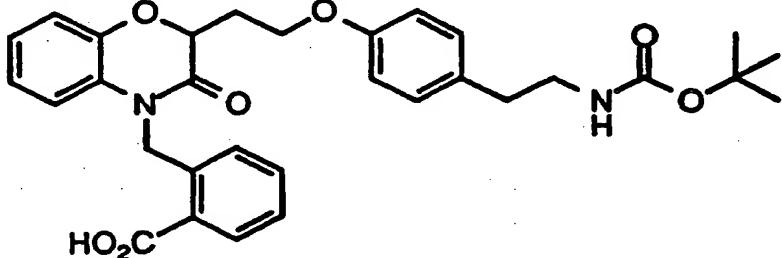
25 3-{3,4-Dihydro-2-[2-(4-(2-aminoethyl)phenoxy)]ethyl-3-oxo-2H-1,4-benzoxazin-4-yl)methylbenzoic acid



Prepared from Compound 111 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated as white crystals in 92% yield, mp 193-195 °C; ^1H NMR (DMSO- d_6) δ 13.03 (br s, 1H), 7.87 (br s, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.77 (br s, 3H), 7.51 (d, J = 7.9 Hz, 1H), 7.47 (q, J = 7.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.04-7.07 (m, 2H), 6.98-7.01 (m, 2H), 6.94 (d, J = 8.5 Hz, 2H), 5.24 (s, 2H), 4.98 (dd, J = 4.2, 8.8 Hz, 1H), 4.17-4.20 (m, 2H), 2.98-3.03 (m, 2H), 2.78 (t, J = 7.8 Hz, 2H), 2.36-2.43 (m, 1H), 2.21-2.34 (m, 1H). IR 2800-3200 (br), 1677, 1636 cm $^{-1}$. MS 447 (MH $^+$), 429, 194 (base). Anal. Calc'd. for C₂₆H₂₆N₂O₅/C₂HF₃O₂/0.5H₂O: C, 59.05; H, 4.96; N, 4.92. Found: C, 58.74; H, 4.87; N, 4.69.

Compound 113

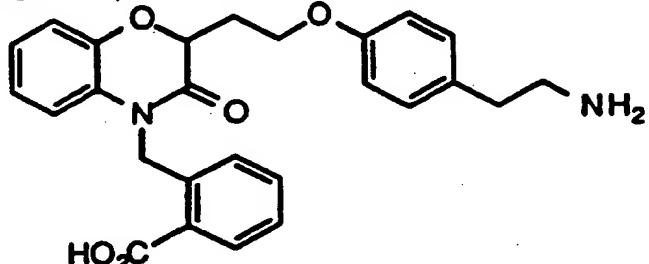
2-[2-[2-(4-(2-(t -butoxycarbonylamino)ethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-4-yl)methylbenzoic acid



Prepared from Compound 107 by method O and isolated as a white powder in 93.5% yield, mp 156-159°C; ^1H NMR (CDCl₃/DMSO- d_6) δ 8.13 (d, J = 7.4 Hz, 1H), 7.32-7.40 (m, 3H with 1H exchangeable), 7.11 (d, J = 8.0 Hz, 2H), 6.97-7.05 (m, 3H), 6.86 (d, J = 8.0 Hz, 2H), 6.72-6.85 (m, 2H), 5.61 (d, J = 18.1 Hz, 1H), 5.53 (d, J = 18.1 Hz, 1H), 4.91 (dd, J = 3.7, 9.3 Hz, 1H), 4.65 (br s, 1H), 4.14-4.22 (m, 2H), 3.23-3.28 (br m, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.47-2.51 (m, 1H), 2.25-2.33 (m, 1H), 1.38 (s, 9H). IR 3350-3500 (br), 2950, 1687, 1512 cm $^{-1}$. MS (FAB) 547 (MH $^+$), 447 (base), 310. Anal. Calc'd. for C₃₁H₃₄N₂O₇/0.50H₂O: C, 67.01; H, 6.35; N, 5.04. Found: C, 67.24; H, 6.56; N, 5.02.

Compound 114

2-[2-[2-(4-(2-Aminoethyl)phenoxy)]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-4-yl)methylbenzoic acid

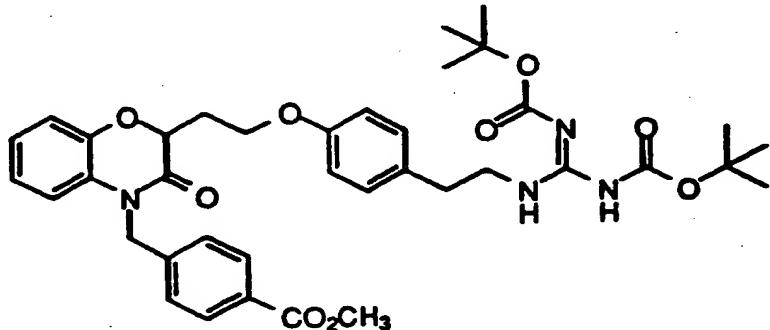


- 5 Prepared from Compound 113 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated as a white solid in 76.8% yield, mp 132-133°C; ¹H NMR (DMSO-*d*₆) δ 8.00 (d, *J* = 6.4 Hz, 1H), 7.74 (br s, 3H), 7.47 (t, *J* = 6.5 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.91-7.09 (m, 6H with a 2H doublet (*J* = 8.5 Hz) at δ 6.95), 6.79 (d, *J* = 2.3 Hz, 1H), 5.53 (d, *J* = 18.4 Hz, 1H), 5.42 (d, *J* = 18.4 Hz, 1H), 5.04 (dd, *J* = 4.0, 8.5 Hz, 1H), 4.18-4.24 (m, 2H), 2.95-3.09 (m, 2H), 2.75-2.81 (m, 2H), 2.23-2.42 (m, 2H). IR 2950-3200 (br), 1683, 1514 cm⁻¹. MS 447 (MH⁺), 138 (base). Anal. Calc'd. for C₂₆H₂₆N₂O₅/1.0C₂H₂O₂/0.25 H₂O: C, 59.52; H, 4.91; N, 4.96. Found: C, 59.43; H, 4.91; N, 4.80.
- 10

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Compound 115

2-[2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(4-carbomethoxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



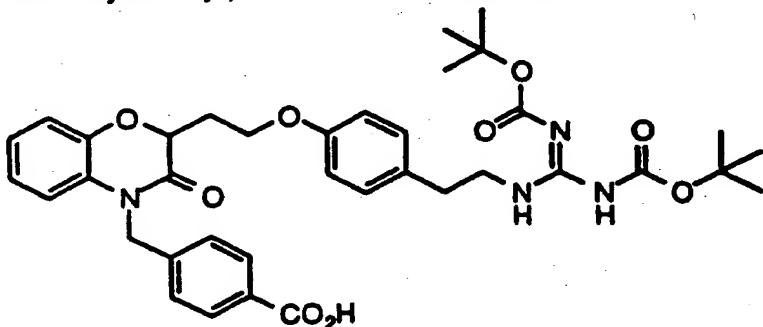
- 20 Prepared by methods L using intermediate 11758-71-2 (Reference Example 81) and *N,N*'-di-*tert*-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine and isolated, after chromatography (eluting with EtOAc/hexanes), as a white glass, mp 68-71°C; ¹H NMR (CDCl₃) δ 11.45 (br s, 1H), 8.37 (br s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.74-7.01 (m, 6H with a 2H doublet (*J* = 8.6 Hz) at δ 6.85), 5.23 (d, *J* = 16.1 Hz, 1H), 5.16 (d, *J* = 16.1 Hz, 1H), 4.95 (dd, *J* = 3.8, 9.5 Hz, 1H), 4.19-
- 25

4.28 (m, 2H), 3.90 (s, 3H), 3.61-3.65 (m, 2H), 2.81 (t, $J = 7.2$ Hz, 2H), 2.55-2.63 (m, 1H), 2.31-2.38 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H). IR 2950-3300 (br), 1724, 1688, 1639 cm^{-1} . MS (FAB) 703 (MH^+), 503 (base). Anal. Calc'd. for $\text{C}_{38}\text{H}_{46}\text{N}_4\text{O}_9/0.5\text{H}_2\text{O}$: C, 64.12; H, 6.66; N, 7.87. Found: C, 63.73; H, 6.87;

5 N, 8.31.

Compound 116

2-[2-[4-[2-(*t*-Butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-4-(4-carboxybenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine

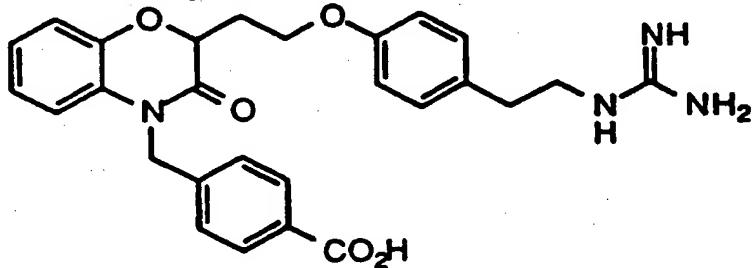


10

Prepared from Compound 115 by method O. The resulting white semisolid was collected, washed with water and dried. NMR shows ~10% methyl ester present. ^1H NMR ($\text{DMSO}-d_6$) δ 7.89 (d, $J = 8.2$ Hz, 2H), 7.37 (d, $J = 8.2$ Hz, 2H), 6.88-7.08 (m, 8H), 5.27 (d, $J = 16.6$ Hz, 1H), 5.19 (d, $J = 16.6$ Hz, 1H), 5.00 (dd, $J = 4.0, 8.7$ Hz, 1H), 3.50-3.61 (m, 2H), 2.65-2.69 (m, 2H), 2.35-2.45 (m, 1H), 2.21-2.30 (m, 1H), 1.37 (s, 9H). MS (FAB) 589 (MH^+), 489 (base).

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Compound 117
4-(4-Carboxybenzyl)-2-[2-[4-[2-(guanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine



25

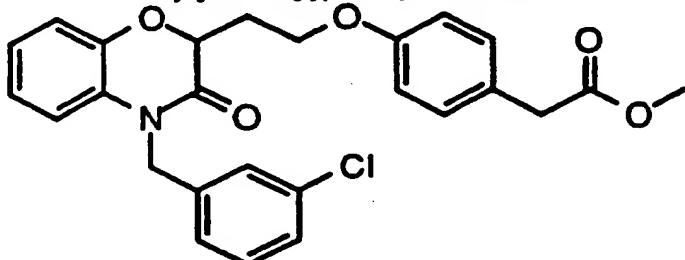
Prepared from Compound 116 by method K using trifluoroacetic acid with anisole present, instead of IPA/HCl and isolated to give an off-white solid, in 67% yield mp 197-199°C; ^1H NMR ($\text{DMSO}-d_6$) δ 7.91 (d, $J = 8.3$ Hz, 2H), 7.76 (br s, 1H), 7.51 (br t, $J = 5$ Hz, 1H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.5$ Hz, 2H), 6.92-7.09 (m, 9H), 5.29 (d, $J = 17.0$ Hz, 1H), 5.23 (d, $J = 17.0$ Hz,

1H), 5.01 (dd, $J = 4.1, 8.6$ Hz, 1H), 4.18-4.23 (m, 2H), 3.30-3.39 (m, 2H), 3.01 (br.s, 1H), 2.62-2.81 (m, 2H), 2.35-2.43 (m, 1H), 2.20-2.31 (m, 1H). IR 3000-3400 (br), 1676, 1501 cm^{-1} . MS (FAB) 489 (MH^+). Anal. Calc'd. for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_5/1.0 \text{C}_2\text{HF}_3\text{O}_2/0.5 \text{H}_2\text{O}$: C, 56.95; H, 4.94; N, 9.16. Found: C, 5 57.32; H, 4.96; N, 8.78.

Compound 118

Methyl 4-[2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-

2-yl]ethoxy]phenyl acetate

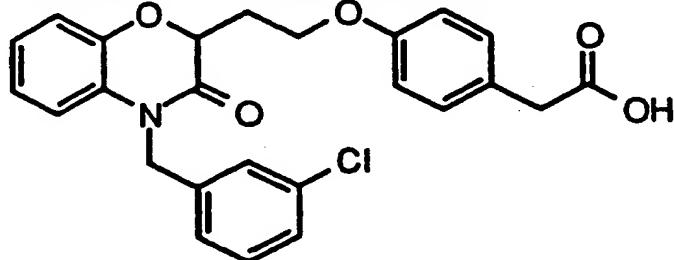


10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl-4-hydroxyphenylacetate at reflux overnight, and isolating a white solid in 38% yield, mp 94-95°C; ^1H NMR (CDCl_3) δ 7.13-7.25 (m, 5H), 7.03-7.11 (m, 1H), 6.81-7.01 (m, 6H), 5.17 (d, $J = 16.2$ Hz, 1H), 5.08 (d, $J = 16.2$ Hz, 1H), 4.94 (dd, $J = 3.9, 9.4$ Hz, 1H), 4.16-4.30 (m, 2H), 3.67 (s, 3H), 3.57 (s, 2H), 2.53-2.64 (m, 1H), 2.33 (ddt, $J = 9.6, 14.5, 4.8$ Hz, 1H). IR 1736, 1673, 1502 cm^{-1} . MS 466 (MH^+), 300 (base). Anal. Calc'd. for $\text{C}_{26}\text{H}_{24}\text{ClNO}_5$: C, 67.02; H, 5.19; N, 3.01. Found: C, 66.78; H, 5.20; N, 2.94.

15

Compound 119

4-[2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-2-yl]ethoxy]phenyl acetic acid



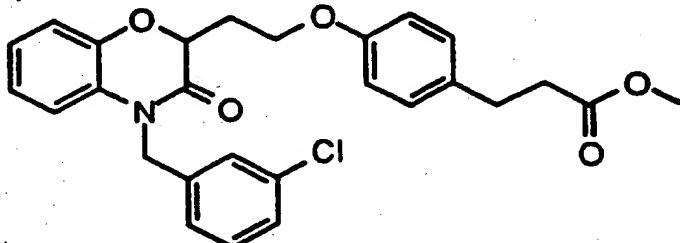
20 25 Prepared from Compound 118 by method O but was acidified with concentrated HCL to afford the acid as a white solid in 95% yield, mp 144-145°C; ^1H NMR ($\text{DMSO}-d_6$) δ 7.19-7.24 (m, 5H), 7.11-7.13 (m, 1H), 6.88-

7.01 (m, 5H), 6.83 (d, $J = 7.3$ Hz, 1H), 5.16 (d, $J = 16.3$ Hz, 1H), 5.07 (d, $J = 16.3$ Hz, 1H), 4.93 (dd, $J = 5.4, 9.4$ Hz, 1H), 4.19-4.23 (m, 2H), 3.61 (s, 2H), 2.51-2.58 (m, 1H), 2.31-2.34 (m, 1H). IR 3000-3200 (br), 1714, 1609 cm^{-1} . MS 452 (MH^+). Anal. Calc'd. for $\text{C}_{25}\text{H}_{22}\text{ClNO}_5$: C, 66.45; H, 4.91; N, 3.10.

5 Found: C, 66.15; H, 4.66; N, 3.03.

Compound 120

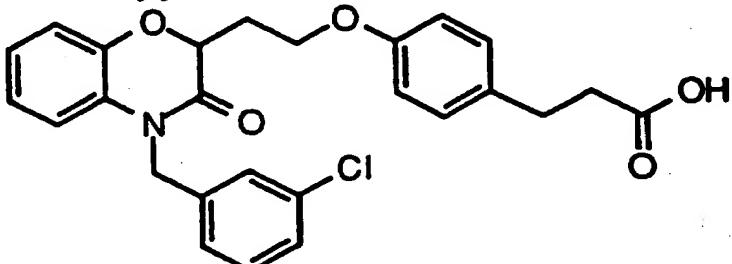
Methyl 3-{4-[2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenyl}propionate



10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl-3-(4-hydroxyphenyl)propionate at reflux overnight, and isolating a white solid in 45% yield, mp 88-89°C; ^1H NMR (CDCl_3) δ 7.14-7.25 (m, 3H), 7.10 (d, $J = 45$ Hz, 2H), 6.93-7.00 (m, 4H), 6.80-6.86 (m, 3H), 5.15 (d, $J = 16.3$ Hz, 1H), 5.09 (d, $J = 16.3$ Hz, 1H), 4.94 (dd, $J = 4.0, 9.8$ Hz, 1H), 4.18-4.23 (m, 2H), 3.67 (s, 3H), 2.89 (t, $J = 7.8$ Hz, 2H), 2.52-2.62 (m, 3H), 2.21-2.28 (m, 1H). IR 1734, 1677, 1502 cm^{-1} . MS 480 (MH^+). Anal. Calc'd. for $\text{C}_{27}\text{H}_{26}\text{ClNO}_5/0.25 \text{H}_2\text{O}$: C, 66.94; H, 5.51; N, 2.89. Found: C, 66.75; H, 5.36; N, 2.82.

Compound 121

3-{4-[2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenyl}propionic acid

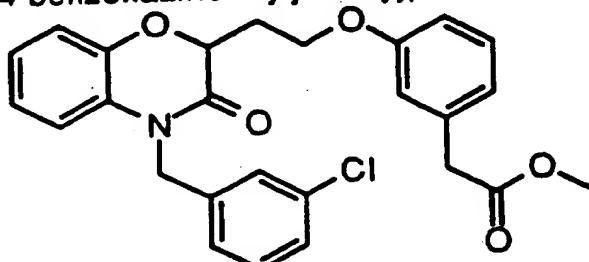


25 Prepared from Compound 120 by method O but was acidified with conc. HCl and isolated as a white solid in 90% yield, mp 141-143 C; ^1H NMR ($\text{DMSO}-d_6$) δ 7.30-7.41 (m, 3H), 7.20-7.23 (m, 1H), 7.16 (d, $J = 8.1$ Hz, 2H),

6.93-7.10 (m, 4H), 6.87 (d, $J = 8.1$ Hz, 2H), 5.23 (d, $J = 16.0$ Hz, 1H), 5.15 (d, $J = 16.0$ Hz, 1H), 5.00 (dd, $J = 4.2, 8.9$ Hz, 1H), 4.10-4.21 (m, 2H), 2.68-2.75 (m, 3H), 2.30-2.52 (m, 3H), 2.12-2.27 (m, 1H). IR 2900-3100 (br), 1721, 1686, 1502 cm⁻¹. MS 466 (MH⁺), 300 (base). Anal. Calc'd. for C₂₆H₂₄CINO₅/0.5 H₂O: C, 65.75; H, 5.31; N, 2.95. Found: C, 65.97; H, 5.05; N, 2.89.

Compound 122

Methyl 3-{2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-2-yl]ethoxy}phenyl acetate

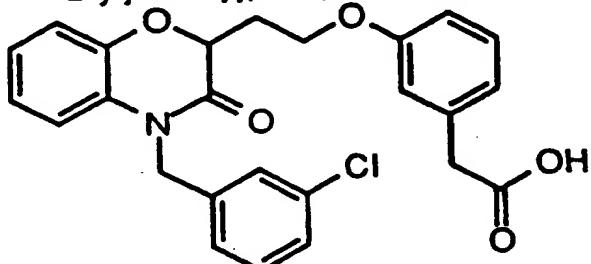


10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl 3-hydroxyphenylacetate at reflux overnight, to give a white solid in 48% yield, mp 80-82°C; ¹H NMR (CDCl_3) δ 7.13-7.24 (m, 6H), 6.81-7.01 (m, 6H), 5.17 (d, $J = 16.2$ Hz, 1H), 5.08 (d, $J = 16.2$ Hz, 1H), 4.94 (dd, $J = 3.8, 9.3$ Hz, 1H), 4.20-4.28 (m, 2H), 3.70 (s, 3H), 3.60 (s, 2H), 2.57-2.61 (m, 1H), 2.29-2.37 (m, 1H). IR 1735, 1680, 1503 cm⁻¹. MS 466 (MH⁺). Anal. Calc'd. for C₂₆H₂₄CINO₅: C, 67.02; H, 5.19; N, 3.01. Found: C, 66.66; H, 5.31; N, 2.90.

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Compound 123

3-{2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine-2-yl]ethoxy}phenyl acetic acid



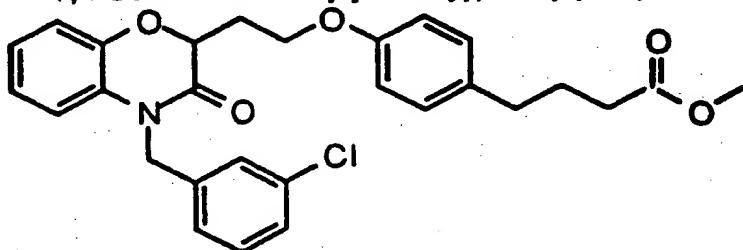
25 Prepared from Compound 122 by method O but was acidified with conc. HCl and isolated as a light pink amorphous solid in 87% yield. ¹H NMR ($\text{DMSO}-d_6$) δ 7.22-7.29 (m, 4H), 7.10-7.13 (m, 1H), 6.80-7.03 (m, 7H), 5.17 (d, $J = 16.3$ Hz, 1H), 5.07 (d, $J = 16.3$ Hz, 1H), 4.94 (dd, $J = 3.9, 9.3$ Hz, 1H),

4.20-4.28 (m, 2H), 3.63 (s, 2H), 2.53-2.59 (m, 1H), 2.33 (ddt, $J = 14.5, 9.5, 4.8$ Hz, 1H). IR 2950-3100 (br), 1728, 1659, 1502 cm⁻¹. MS 452 (MH⁺). Anal. Calc'd. for C₂₅H₂₂ClNO₅/0.6 H₂O: C, 64.89; H, 5.05; N, 3.03. Found: C, 64.62; H, 4.91; N, 2.95.

5

Compound 124

Methyl 4-{4-[2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenyl}butyrate

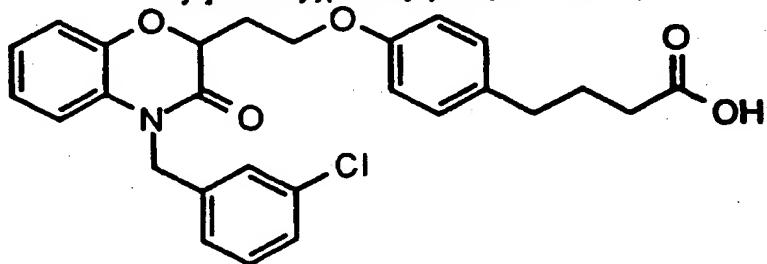


- 10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl 3-(4-hydroxyphenyl)butyrate at reflux overnight, and isolating a clear, amorphous solid in 46% yield; ¹H NMR (CDCl₃) δ 7.10-7.20 (m, 3H), 6.99-7.08 (m, 3H with a 2H doublet ($J = 8.5$ Hz) at δ 7.03), 6.83-6.94 (m, 3H), 6.75-6.80 (m, 3H with a 2H doublet ($J = 8.5$ Hz) at δ 6.78), 5.09 (d, $J = 16.4$ Hz, 1H), 5.00 (d, $J = 16.4$ Hz, 1H), 4.94 (dd, $J = 3.9, 9.2$ Hz, 1H), 4.10-4.25 (m, 2H), 3.60 (s, 3H), 2.41-2.52 (m, 3H), 2.20-2.35 (m, 3H), 1.89 (quintet, $J = 7.5$ Hz, 2H). IR 1732, 1681, 1502 cm⁻¹. MS 494 (MH⁺).
- 15

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Compound 125

4-{4-[2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenyl}butyric acid



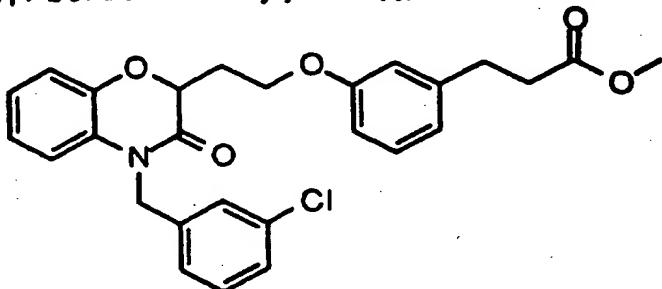
- 25 Prepared from Compound 124 by Method O but acidified with conc. HCl and isolated as a white solid in 83% yield, mp 129-130°C; ¹H NMR (DMSO- d_6) δ 6.99-7.25 (m, 7H with a 2H doublet ($J = 8.5$ Hz) at δ 7.10), 6.91-6.96 (m, 3H), 6.81-6.87 (m, 3H with a 2H doublet ($J = 8.5$ Hz) at δ 6.84), 5.16 (d, $J = 16.3$ Hz, 1H), 5.08 (d, $J = 16.3$ Hz, 1H), 4.94 (dd, $J = 3.8, 9.4$ Hz, 1H), 4.18-

4.26 (m, 2H), 2.58-2.64 (m, 3H), 2.25-2.39 (m, 3H), 1.94 (quintet, $J = 7.5$ Hz, 2H). - IR 2900-3050 (br), 1697, 1678, 1503 cm^{-1} . MS 480 (MH^+), 422 (base). Anal. Calc'd. for $\text{C}_{27}\text{H}_{26}\text{ClNO}_5$: C, 67.57; H, 5.46; N, 2.92. Found: C, 67.19; H, 5.39; N, 2.78.

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Compound 126

Methyl 3-[3-[2-{4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl}ethoxy]phenyl]propionate

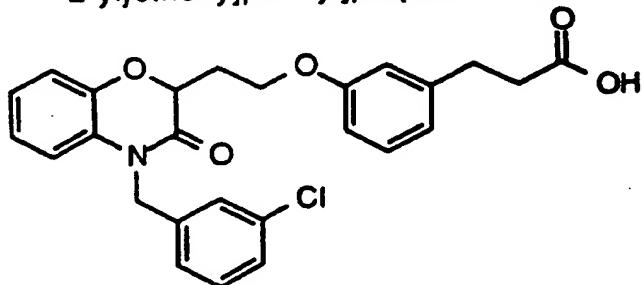


- 10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl 3-(3-hydroxyphenyl)propionate at reflux overnight, and isolating a white solid in 51% yield, mp 92-94°C; ^1H NMR (CDCl_3) δ 6.91-7.24 (m, 8H), 6.76-6.83 (m, 4H), 5.18 (d, $J = 16.1$ Hz, 1H), 5.08 (d, $J = 16.1$ Hz, 1H), 4.94 (dd, $J = 3.9, 9.4$ Hz, 1H), 4.21-4.28 (m, 2H), 3.68 (s, 3H), 2.93 (t, $J = 7.8$ Hz, 2H), 2.63 (t, $J = 7.8$ Hz, 2H), 2.53-2.59 (m, 1H), 2.33 (ddt, $J = 9.4, 14.2, 4.7$ Hz, 1H). IR 1724, 1677, 1503 cm^{-1} . MS 480 (MH^+). Anal. Calc'd. for $\text{C}_{27}\text{H}_{26}\text{ClNO}_5$: C, 67.57; H, 5.46; N, 2.92. Found: C, 67.38; H, 5.51; N, 2.71.
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Compound 127

3-[3-[2-{4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl}ethoxy]phenyl]propionic acid

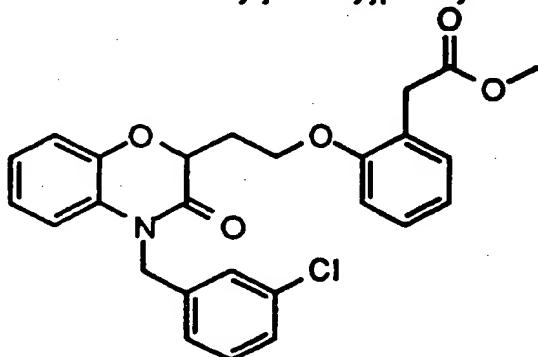


- 25 Prepared from Compound 126 by method O but acidified with conc. HCl and isolated as a white solid in 93% yield, mp 118-119°C; ^1H NMR ($\text{DMSO}-d_6$) δ 7.18-7.24 (m, 4H), 7.10-7.12 (m, 1H), 6.90-7.04 (m, 3H), 6.77-6.83 (m,

4H), 5.16 (d, $J = 16.0$ Hz, 1H), 5.07 (d, $J = 16.0$ Hz, 1H), 4.95 (dd, $J = 3.8, 9.6$ Hz, 1H), 4.21-4.29 (m, 2H), 2.94 (t, $J = 7.5$ Hz, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 2.53-2.57 (m, 1H), 2.32 (ddt, $J = 9.8, 14.5, 4.7$ Hz, 1H). IR 3000-3200 (br), 1691, 1679, 1501 cm^{-1} . MS 466 (MH^+). Anal. Calc'd. for $\text{C}_{26}\text{H}_{24}\text{ClNO}_5$: C, 67.02; H, 5.19; N, 3.01. Found: C, 66.63; H, 5.17; N, 2.87.

Compound 128

Methyl 2-{2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenylacetate



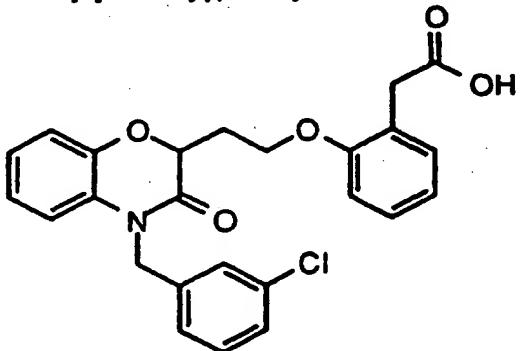
10

Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with methyl 2-hydroxyphenylacetate at reflux overnight, and isolating a yellow oil. ^1H NMR (CDCl_3) δ 7.09-7.39 (m, 6H), 6.81-7.04 (m, 6H), 5.18 (d, $J = 16.3$ Hz, 1H), 5.07 (d, $J = 16.3$ Hz, 1H), 4.92 (dd, $J = 3.8, 9.6$ Hz, 1H), 4.21-4.32 (m, 2H), 3.60 (s, 2H), 2.54-2.62 (m, 2H), 2.33 (ddt, $J = 14.4, 9.6, 4.9$ Hz, 1H).

Compound 129

2-{2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenylacetic acid

20



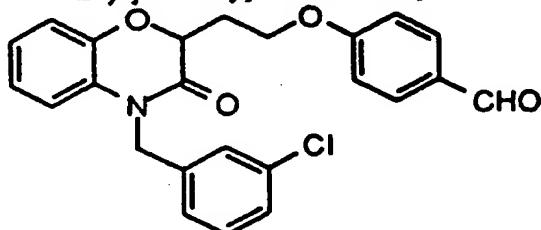
Prepared from Compound 128 by method O but acidified with conc. HCl and isolated as a white solid in 89% yield, mp 140-142°C; ^1H NMR (DMSO-D_6)

d₆) δ 7.07-7.25 (m, 6H), 6.84-7.00 (m, 6H), 5.13 (s, 2H), 5.01 (dd, J = 4.0, 9.2 Hz, 1H), 4.20-4.34 (m, 2H), 3.68 (d, J = 16.0 Hz, 1H), 3.59 (d, J = 16.0 Hz, 1H), 2.40-2.59 (m, 1H), 2.28-2.38 (m, 1H). IR 3000-3200 (br), 1722, 1677, 1498 cm⁻¹. MS 452 (MH⁺), 300 (base). Anal. Calc'd. for C₂₅H₂₂ClNO₅/0.2 H₂O: C, 65.92; H, 4.96; N, 3.07. Found: C, 65.75; H, 4.99; N, 2.88.

5 H₂O: C, 65.92; H, 4.96; N, 3.07. Found: C, 65.75; H, 4.99; N, 2.88.

Compound 130

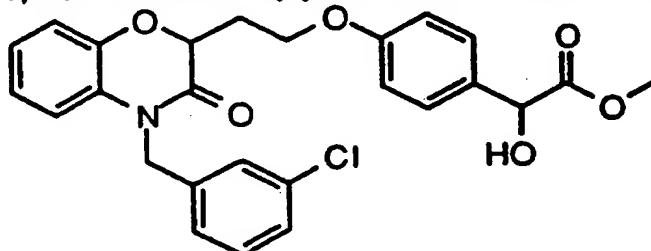
4-[2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy]benzaldehyde



10 Prepared from method L, which was modified by coupling intermediate 10488-22 (Reference Example 66) with 4-hydroxybenzaldehyde at reflux overnight. The product was isolated as a white solid after chromatography in 30% yield, mp 130-131°C; ¹H NMR (CDCl₃) δ 9.89 (s, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.23-7.30 (m, 3H), 7.10-7.15 (m, 1H), 6.92-7.05 (m, 5H), 6.83 (dd, J = 1.4, 8.7 Hz, 1H), 5.20 (d, J = 16.2 Hz, 1H), 5.07 (d, J = 16.2 Hz, 1H), 4.93 (dd, J = 4.1, 9.1 Hz, 1H), 4.25-4.42 (m, 2H), 2.58-2.70 (m, 1H), 2.40 (ddt, J = 10.0, 14.2, 5.0 Hz, 1H). IR 1700, 1674, 1598 cm⁻¹. MS 422 (MH⁺). Anal. Calc'd. for C₂₄H₂₀ClNO₄: C, 68.33; H, 4.78; N, 3.32. Found: C, 68.01; H, 4.82; N, 3.27.

Compound 131

Methyl 2-[4-[2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy]phenyl]glycolate

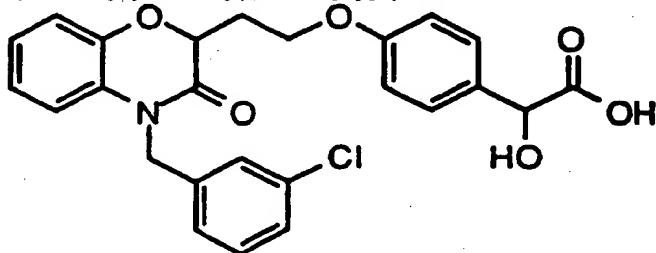


25 Bromoform (0.31 mL, 3.54 mmol) was added dropwise under a nitrogen atmosphere to Compound 130 (1.15 g, 2.73 mmol), lithium chloride (0.231 g, 5.45 mmol), potassium hydroxide (0.611 g, 10.9 mmol) and water (4 mL) in

dioxane (4 mL). After heating in an oil bath at 40 °C overnight, the reaction was acidified to pH=1 with HCl (1 N) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), dried (MgSO_4), filtered and evaporated to afford impure hydroxyacid as a yellow oil. A solution of acetyl chloride (0.4 mL) in methanol (10 mL) was added to the crude acid and the reaction stirred at room temperature under a nitrogen atmosphere overnight. The methanol was evaporated and the residue dissolved in ether (200 mL). This was washed with saturated NaHCO_3 (2 x 50 mL), dried (MgSO_4), filtered and evaporated. The α -hydroxyester was obtained after silica gel chromatography (eluting with $\text{EtOAc}/\text{CH}_2\text{Cl}_2$), in 52% overall yield, ^1H NMR (CDCl_3) δ 7.32 (d, $J = 8.7$ Hz, 2H), 7.23-7.26 (m, 3H), 7.10-7.15 (m, 1H), 6.93-7.03 (m, 3H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.81-6.89 (m, 1H), 5.18 (d, $J = 16.2$ Hz, 1H), 5.13 (d, $J = 5.6$ Hz, 1H), 5.07 (d, $J = 16.2$ Hz, 1H), 4.93 (dd, $J = 3.9, 9.4$ Hz, 1H), 4.17-4.32 (m, 2H), 3.76 (s, 3H), 3.40 (d, $J = 5.6$ Hz, 1H, exchangeable), 2.53-2.64 (m, 1H), 2.33 (ddt, $J = 14.4, 9.4, 4.8$ Hz, 1H).

Compound 132

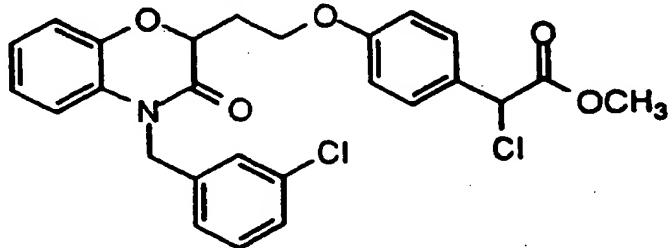
2-[4-{2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-
y]ethoxy}phenyl]glycolic acid



Prepared from Compound 131 by method O but acidified with conc. HCl and isolated as a pale yellow solid, in 85% yield, mp 54-56°C; ^1H NMR ($\text{DMSO}-d_6$) δ 7.36 (d, $J = 8.6$ Hz, 2H), 7.23-7.26 (m, 4H), 7.09-7.12 (m, 1H), 6.81-7.01 (m, 5H), 5.20 (s, 1H), 5.16 (d, $J = 16.6$ Hz, 1H), 5.07 (d, $J = 16.6$ Hz, 1H), 4.93 (dd, $J = 4.0, 9.2$ Hz, 1H), 4.20-4.27 (m, 2H), 3.20 (br s, 1H, exchangeable), 2.53-2.62 (m, 1H), 2.30-2.38 (m, 1H). IR 3300-3400 (br), 2800-3150 (br), 1731, 1671, 1512 cm^{-1} . MS (FAB) 468 (MH^+), 300 (base). Anal. Calc'd. for $\text{C}_{25}\text{H}_{22}\text{ClNO}_6/0.5 \text{H}_2\text{O}$: C, 62.96; H, 4.86; N, 2.94. Found: C, 62.80; H, 4.99; N, 2.92.

Compound 133

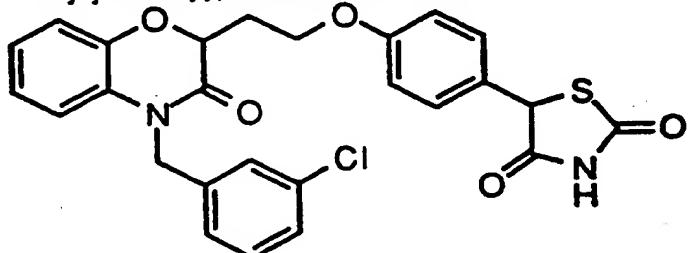
Methyl 2-chloro-2-[4-(2-[4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy)phenyl]acetate



- 5 Thionyl chloride (0.091 mL, 1.24 mmol) was added to Compound 130 (0.460 g, 0.95 mmol) in benzene (10 mL), followed by pyridine (0.093 mL, 1.15 mmol) under a nitrogen atmosphere at room temperature. After stirring overnight, the solvent was evaporated and the residue poured into water (50 mL). This mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (3 x 50 mL), dried (MgSO_4), filtered and evaporated to afford corresponding chloride as a clear gel in 82% yield; ^1H NMR ($\text{DMSO}-d_6$) δ 7.42 (d, $J = 8.7$ Hz, 2H), 7.23-7.29 (m, 3H), 7.11-7.15 (m, 1H), 6.99-7.03 (m, 2H), 6.90-6.97 (m, 3H with a 2H doublet ($J = 8.7$ Hz) at δ 6.92), 6.82 (d, $J = 7.4$ Hz, 1H), 5.34 (s, 1H), 5.18 (d, $J = 16.2$ Hz, 1H), 5.08 (d, $J = 16.2$ Hz, 1H), 4.93 (dd, $J = 4.0, 9.4$ Hz, 1H), 4.19-4.33 (m, 2H), 3.78 (s, 3H), 2.54-2.65 (m, 1H), 2.34 (ddt, $J = 14.3, 9.4, 4.8$ Hz, 1H).
- 10
- 15

Compound 134

20 5-[4-{2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy}phenyl]thiazolidine-2,4-dione

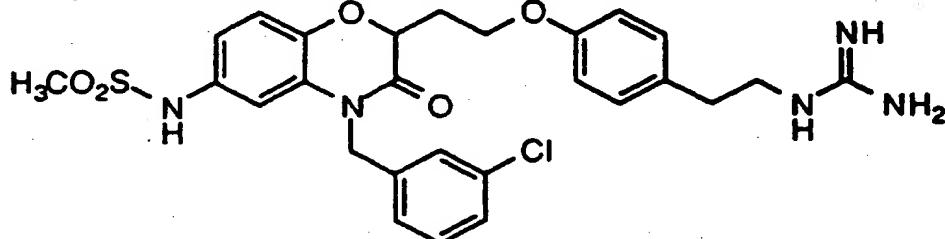


- 25 Thiourea (56 mg, 0.74 mmol) was added to Compound 133 (0.185 g, 0.37 mmol) in 2-methoxyethanol (3 mL). The reaction was heated in an oil bath at 110 °C for 3 h. After cooling, HCl (1 N, 2.5 mL) was added to the reaction and heated at 100 °C overnight. The cooled reaction was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were washed with water (3 x 50 mL), dried (MgSO_4), filtered and evaporated to

afford the thiazolidindione as pale yellow foam in 64% yield, mp 70-72 C; ¹H NMR (DMSO-d₆) δ 8.05 (br s, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.23-7.25 (m, 3H), 7.11-7.15 (m, 1H), 6.81-7.02 (m, 5H with a 2H doublet (J = 8.7 Hz) at δ 6.96), 6.83 (d, J = 8.6 Hz, 1H), 5.36 (s, 1H), 5.19 (d, J = 16.2 Hz, 1H), 5.07 (d, J = 16.2 Hz, 1H), 4.94 (dd, J = 4.0, 9.1 Hz, 1H), 4.22-4.30 (m, 2H), 2.54-2.62 (m, 1H), 2.32-2.40 (m, 1H). IR 1756, 1698, 1500 cm⁻¹. MS 509 (MH⁺).

Compound 135

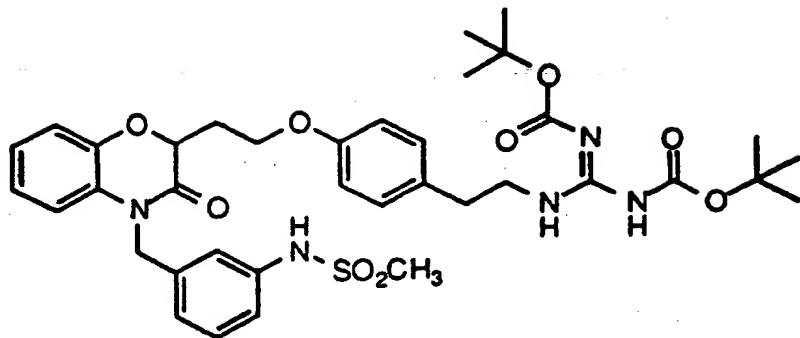
10 3,4-Dihydro-2-{2-[4-(2-guanidinoethyl)phenoxy]ethyl}-
6-methylsulfonamido-4-(3-chlorobenzyl)-3-oxo-2H-1,4-benzoxazine



Method P: Compound 92 was heated at reflux for 10 hours with methanesulfonyl chloride (1.1 eq) DMAP (0.1 eq) in CH₂Cl₂ (10 mL). The resulting mixture was diluted with water and title compound was isolated by filtration, mp (dec) >121°C; IR (KBr) 3240, 1667, 1613, 1512, 1475, 1349, 1245, 1178, 865 cm⁻¹; ¹H NMR (DMSO-d₆) δ 9.63 (br s, 1H), 8.07 (br s, 1H), 7.43 (br s, 2H), 7.35 (m, 4H), 7.20 (m, 3H), 7.01 (d, 1H, J = 8.6Hz), 6.89 (m, 2H), 6.82 (dd, 2H, J = 2.2, 8.5Hz), 5.16 (d, 1H, J = 16.5Hz), 5.03 (d, 1H, J = 16.5Hz), 4.97 (dd, 1H, J = 4.2, 8.8Hz), 4.16 (m, 2H), 3.25 (m, 2H), 2.79 (s, 3H), 2.70 (t, 2H, J = 7.2Hz), 2.35 (m, 1H), 2.22 (m, 1H). Anal. Calc'd for C₂₇H₃₀CIN₅O₅S · 1.7 HCl: C 51.15, H 5.04, N 11.05. Found: 51.47, H 5.14, N 10.78.

Compound 136

25 2-{2-[4-(2-(N,N-Bis-*tert*-butoxycarbonylguanidino)ethyl)phenoxy]ethyl}-
3,4-dihydro-4-(3-methylsulfonamidobenzyl)-3-oxo-2H-1,4-benzoxazine



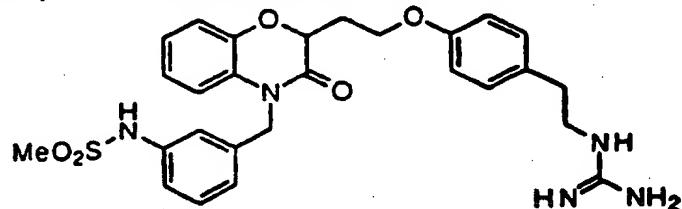
Prepared from Compound 101 by method P to give a tan solid (dec) $>79^\circ\text{C}$; MS (FAB) $\text{MH}^+ 738$; IR (KBr) 3325, 2977, 1723, 1687, 1612, 1501, 1410, 1330, 1245, 1151, 1057, 971, 688 cm^{-1} ; ^1H NMR (CDCl_3) δ 11.47 (br s, 1H),

- 5 8.37 (br t, 1H), 7.31 (m, 1H), 7.11 (m, 4H), 7.05-6.89 (m, 3H), 6.83 (m, 3H), 6.45 (br s, 1H), 5.14 (d, 2H, $J = 7.2 \text{ Hz}$), 4.94 (dd, 1H, $J = 4.0, 9.3 \text{ Hz}$), 4.20 (m, 2H), 3.62 (m, 2H), 2.94 (s, 3H), 2.81 (t, 2H, $J = 7.2 \text{ Hz}$), 2.55 (m, 1H), 2.34 (m, 1H), 1.60 (br s, 1H), 1.50 (s, 9H), 1.48 (s, 9H). Anal. Calc'd for $\text{C}_{37}\text{H}_{47}\text{N}_5\text{O}_9\text{S}$ - 0.9 H_2O : C 58.93, H 6.52, N 9.29. Found C 59.19, H 6.58, N 9.00.

10

Compound 137

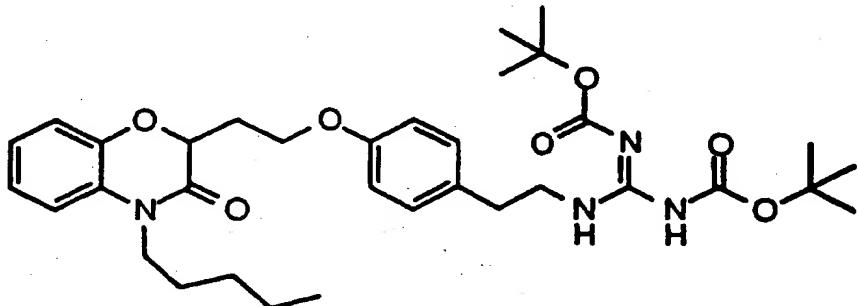
2-{2-[4-(2-Guanidinoethyl)-phenoxy]ethyl}-3,4-dihydro-4-(3-methylsulfonamidobenzyl)-3-oxo-2H-1,4-benzoxazine



- 15 Prepared from Compoud 136 by method K in 94% yield, mp (dec) $>95^\circ\text{C}$; MS (FAB) $\text{MH}^+ 538$; IR (KBr) 3156, 1664, 1500, 1468, 1402, 1327, 1243, 1147, 1052, 978, 751, 690, 514 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ 9.82 (br s, 1H), 7.64 (br t, 1H), 7.55-6.85 (br s, 3H), 7.28 (t, 1H, $J = 7.8 \text{ Hz}$), 7.20 (d, 2H, $J = 8.5 \text{ Hz}$), 7.09 (s, 1H), 7.05 (m, 2H), 6.99 (m, 4H), 6.92 (d, 2H, $J = 8.5 \text{ Hz}$), 5.19 (d, 1H, $J = 16.6 \text{ Hz}$), 5.09 (d, 1H, $J = 16.6 \text{ Hz}$), 4.94 (dd, 1H, $J = 4.11, 9.0 \text{ Hz}$), 4.19 (m, 2H), 3.33 (m, 2H), 2.93 (s, 3H), 2.72 (t, 2H, $J = 7.4 \text{ Hz}$), 2.32 (m, 1H), 2.22 (m, 1H). Anal. Calc'd for $\text{C}_{27}\text{H}_{31}\text{N}_5\text{O}_5\text{S}$: C 55.32, H 5.93, N 11.32. Found: C 55.34, H 5.86, N 11.34.

Compound 138

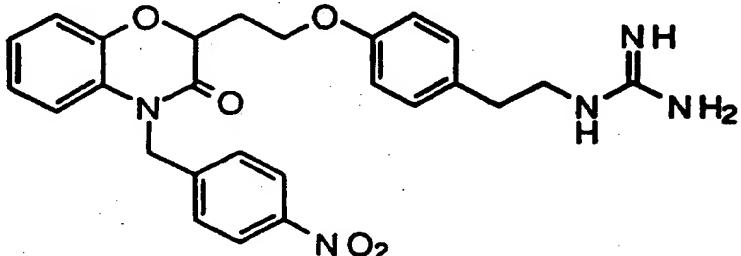
2-[2-[4-[2-(*N,N*-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-3-oxo-4-pentyl-2*H*-1,4-benzoxazine



- 5 Prepared from 10840-185 (Reference Example 60) by method L using equal equivalents of reagents and was isolated in 42% yield as a white foam after SiO₂ chromatography (hexane/CH₂Cl₂, 1/3); IR (KBr) 3334, 2977, 2932, 2872, 1685, 1639, 1615, 1501, 1409, 1366, 1331, 1131, 1058, 748 cm⁻¹; ¹H NMR (CDCl₃) δ 0.91 (t, J = 6.8 Hz, 3H), 1.32-1.40 (m, 4H), 1.48 (s, 9H), 1.51 (s, 9H), 1.61-1.72 (m, 2H), 2.17-2.30 (m, 1H), 2.43-2.55 (m, 1H), 2.81 (t, J = 7.2 Hz, 2H), 3.63 (q, J = 7.1 Hz, 2H), 3.92 (t, J = 6.8 Hz, 2H), 4.13-4.25 (m, 2H), 4.79 (dd, J = 9.20, 4.0 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.96-7.07 (m, 4H), 7.12 (d, J = 8.6 Hz, 2H), 8.37 (br t, J = 4.3 Hz, 1H), 11.48 (br s, 1H); Anal. Calc'd for C₃₄H₄₈N₄O₇: C, 65.36; H, 7.74; N, 8.97. Found: C, 65.23; H, 7.70; N, 8.98.

Compound 139

3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-4-(4-nitrobenzyl)-3-oxo-2*H*-1,4-benzoxazine



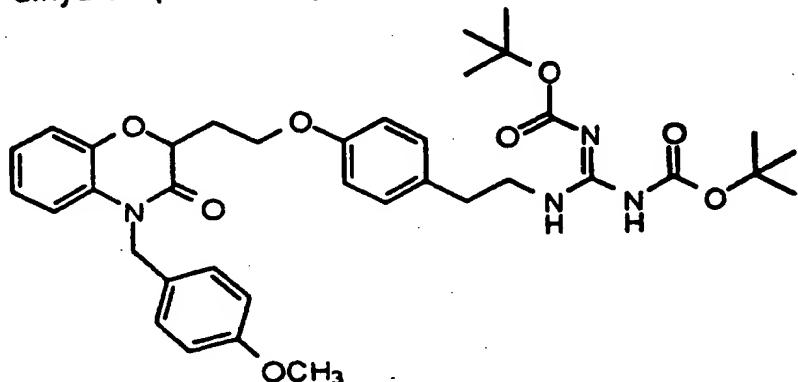
20

- Prepared from Compound 93 by method K to give a solid: in 68% yield: mp: dec.>101°C; MS: FAB MH⁺ at 524; IR (KBr) 3433, 1671, 1600, 1525, 1501, 1468, 1398, 1344, 1253, 1065, 894, 810 cm⁻¹; ¹H NMR (DMSO-d₆/TMS) δ 8.20(d, 2H, J=8.2 Hz), 7.54(d, 2H, J=8.5 Hz), 7.45-6.60(v. br. s., 4H), 7.38(s, 1H), 7.29(s, 1H), 7.18(m, 2H), 7.05(m, 2H), 6.97(m, 3H), 5.36(d, 1H, J=18.0

Hz), 5.22(1H, J=18.0 Hz), 4.99(m, 1H), 4.26(m, 2H), 3.35(m, 2H), 2.68(t, 2H, J=6.3 Hz), 2.40(m, 1H), 2.28(m, 1H).

Compound 140

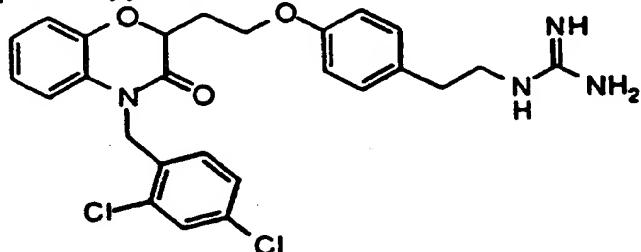
- 5 2-[2-[4-[2-(N,N-Bis-*tert*-butoxycarbonylguanidino)ethyl]phenoxy]ethyl]-3,4-dihydro-4(4-methoxybenzyl)-3-oxo-2*H*-1,4-benzoxazine



- Prepared by method L using intermediate 10508-19 (Reference Example 47) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine to give 10 the title compound as a white foam: Anal. Calc'd for C₂₇H₄₆N₄O₈: C, 65.86; H, 6.87; N, 8.3. Found: C, 65.51; H, 7.02; N, 8.27.

Compound 141

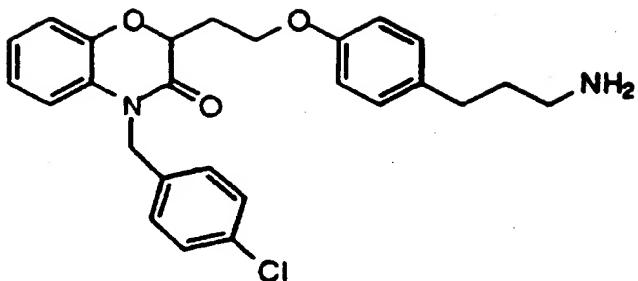
- 15 3,4-Dihydro-4-(2,4-dichlorobenzyl)-2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-3-oxo-2*H*-1,4-benzoxazine



- Prepared by method L using intermediate 10005-181-1 (Reference Example 48) and N,N'-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine and 20 method K to give a solid: Anal. Calc'd for C₂₆H₄₂Cl₂N₄O₃·HCl·0.75 H₂O: C, 55.43; H, 5.10; N, 9.94. Found: C, 55.43; H, 5.05; N, 9.75.

Compound 142

- 2-[2-[4-(3-Aminopropyl)phenoxy]ethyl]-4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazin

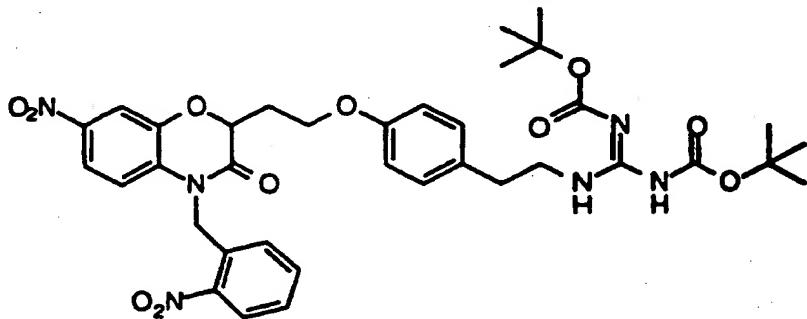


Prepared from intermediate 10353-28-1 (Reference Example 41) and 4-[3-(N-t-butoxycarbonylamino)propyl]phenol by methods J and K to give the title compound as a yellow solid (11% yield). m.p.=95-97°C; MS (FAB) MH^+ 451;

- 5 IR (KBr) 1250, 1400, 1500, 1590, 1680, 2040, 2950, 3400 cm^{-1} ; 1H (NMR) 7.40 (d, $J=8.47Hz$, 2H), 7.30 (d, $J=8.48Hz$, 2H), 2.62 (t, $J=7.54Hz$, 2H), 2.76 (t, $J=7.52Hz$, 2H), 7.23 (t, $J=8.12Hz$, 1H), 6.81 (d, $J=7.37Hz$, 3H), 7.91 (br. s., 2H), 6.99-7.08 (m, 4H), 4.19-4.20 (m, 2H), 2.33-2.49 (m, 1H), 2.19-2.30 (m, 1H), 1.82-1.87 (m, 2H), 5.18 (dd, $J=16.48$ and $23.23Hz$, 2H), 4.98 (dd, $J=4.15$ and $8.75Hz$, 1H). Anal. Calc'd for $C_{26}H_{28}N_2O_3Cl_2$: C 62.68, H 5.91, N 5.62. Found: C 62.97, H 5.78, N 5.37.

Compound 143

2-{2-[4-(2-(*N,N*-Bis-*t*-butoxycarbonylguanidino)ethyl)-phenoxy}ethyl}-3,4-dihydro-7-nitro-4-(2-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine



Prepared by method L using intermediate 11653-142 (Reference Example 69) and *N,N'*-di-*t*-butoxycarbonyl-2(4-hydroxyphenyl)ethyl guanidine, and

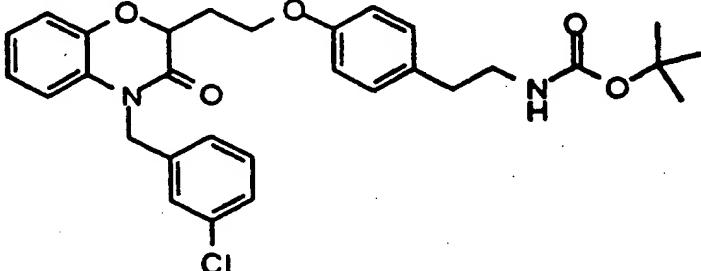
- 20 method K to give the title compound as a solid in 13% yield; m.p.: dec.>128°C; MS (FAB) MH^+ 735; IR (KBr) 3323, 3087, 2977, 1723, 1690, 1641, 1613, 1530, 1513, 1476, 1418, 1395, 1240, 1154, 941 cm^{-1} ; 1H NMR ($CDCl_3/TMS$) δ 11.43(s, 1H), 8.37(br. t., 1H), 8.24(dd, 1H, $J=2.1$, 7.4 Hz), 7.94(d, 1H, $J=2.5$ Hz), 7.84(dd, 1H, $J=2.5$, 8.9 Hz), 7.52(m, 2H), 7.14(d, 2H, $J=8.6$ Hz), 7.08(d, 1H, $J=9.1$ Hz), 6.84(d, 2H, $J=8.6$ Hz), 6.77(d, 1H, $J=8.9$ Hz), 5.68(d, 1H, $J=18.1$ Hz), 5.56(d, 1H, $J=18.1$ Hz), 5.10(dd, 1H, $J=4.0$, 8.9

Hz), 4.23(m, 2H), 3.64(m, 2H), 2.82(t, 2H, J=7.3 Hz), 2.63(m, 1H), 2.40(m, 1H), 1.50(s, 9H), 1.48(s, 9H).

Compound 144

**2-[2-[4-(2-(1-Butoxycarbonylamino)ethyl)phenoxy]ethyl]-
4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine**

5



10

Methanesulfonyl chloride (0.8 ml, 1.5 eq.) was added in one portion to a solution of intermediate 10353-191-1 (2.0 g, 1 eq., Reference Example 40), DMAP (0.33 g, 0.4 eq.) and triethylamine (1.2 ml, 1.5 eq.) in 30 ml CH₂Cl₂. This mixture was stirred for 15 min and diluted with an equal part of water. The resulting organic layer was washed with brine, dried (MgSO₄) and concentrated *in vacuo* to give the mesylate. This mesylate was treated with 4-[2-(N-1-butoxycarbonylamino)ethyl]phenol following the procedures of method J to give the title compound as a solid: mp 91-92 °C.

15

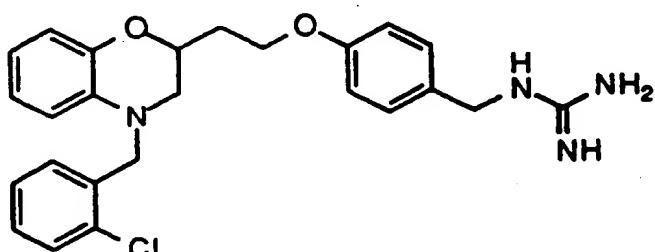
Compound 145

**2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-
4-(2-chlorobenzyl)-6-methyl-3,4-dihydro-2H-1,4-benzoxazine**

20

Prepared by method L using intermediate 10353-76 (Reference Example 89) and N,N'-di-1-butoxycarbonyl-2-(4-hydroxyphenyl)ethyl guanidine and method K with the following modifications. The bis-Boc-protected Mitsunobu coupling product was isolated by dissolving the crude product residue in aqueous methanol and treating with a dropwise addition of 2N NaOH until basic. The precipitate was collected by filtration. The resulting product was dissolved in ether, washed sequentially with 1N HCl, sat'd NaHCO₃, and brine, dried over Na₂SO₄ and concentrated under vacuum and used without

25

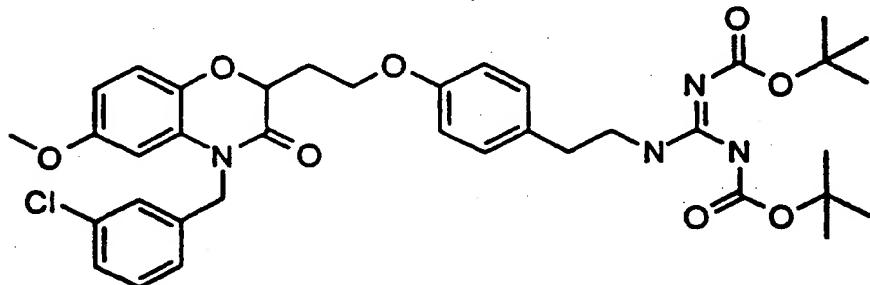


further purification. The deprotected product was isolated the bicarbonate salt (light brown solid) in 22% yield as a tan solid, single homogeneous peak by HPLC (PDA detection) 15cm C18 column, eluting with 55/45 H₂O (5% NH₄OH, 5% HOAC)/CH₃CN; MS (Cl) 451 (MH⁺); IR (KBr) 3314, 3036,

- 5 2923, 1682, 1608, 1581, 1511, 14658, 1443, 1392, 1352, 1302, 1244, 1223, 1175, 1046, 742 cm⁻¹.

Compound 146

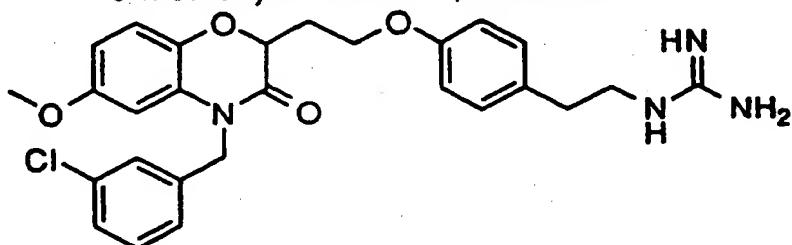
- 10 2-{2-[4-(2-(*N,N*-Bis-*t*-butoxycarbonylguanidino)ethyl)-phenoxy]ethyl}-4-(3-chlorobenzyl)-3,4-dihydro-6-methoxy-3-oxo-2H-1,4-benzoxazine



- Prepared from intermediate 12168-25-1 (Reference Example 43) and *N,N'*-di-*t*-butoxycarbonyl-2(4-hydroxy-phenyl)ethyl guanidine by method L in 92 % yield. Crystallization from EtOH/H₂O afforded the pure product as a white solid. nmr (CDCl₃) δ 11.28 (s, 1H), 7.23 (m, 3H), 7.12 (m, 1H), 7.12 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 9.0 Hz, 2H), 6.51 (dd, J = 8.4, 2.9 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 5.15 (d, J = 16.9 Hz, 1H), 5.05 (d, J = 16.9 Hz, 1H), 4.89 (dd, J = 10.0, 4.1 Hz, 1H), 4.20 (m, 2H), 3.64 (m, 2H), 2.82 (apparent t, J = 7.3 Hz, 2H), 2.55 (m, 1H), 2.32 (m, 1H), 1.52 (s, 9H), 1.50 (s, 9H).

Compound 147

- 25 4-(3-Chlorobenzyl)-3,4-dihydro-2-{2-[4-(2-guanidinoethyl)-phenoxy]ethyl}-6-methoxy-3-oxo-2H-1,4-benzoxazine

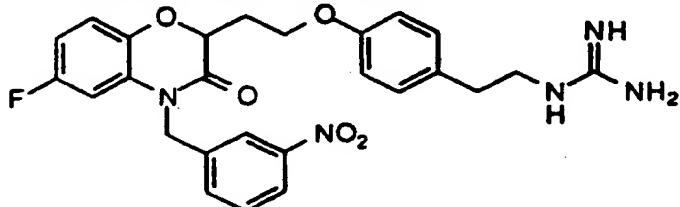


Prepared from Compound 146 by method K and isolated by trituration with Et₂O to afford a hydroscopic tan solid in 76% yield nmr (DMSO-d₆) δ 7.43

(br s, 1H), 7.4-6.5 (v br s, 4H), 7.35 (m, 3H), 7.22 (m, 1H), 7.19 (d, $J = 8.5$ Hz, 2H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.96 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 2.5$ Hz, 1H), 2.58 (dd, $J = 9.0, 3.1$ Hz, 1H), 5.21 (d, $J = 17.0$ Hz, 1H), 5.18 (d, $J = 17.0$ Hz, 1H), 4.96 (dd, $J = 8.8, 4.1$ Hz, 1H), 4.19 (m, 2H), 3.64 (s, 3H), 3.30 (m, 2H), 5 2.40 (apparent t, $J = 6.8$ Hz, 2H), 2.39 (m, 1H), 2.23 (m, 1H).

Compound 148

**2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-
3,4-dihydro-6-fluoro-4-(3-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine**



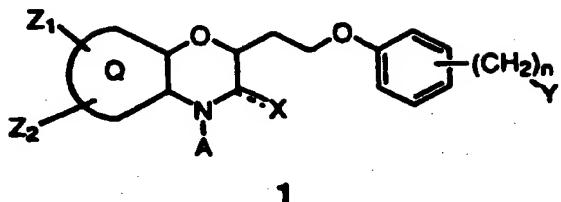
- 10 Prepared from Compound 102 by method K to give the title compound as a solid: MP: dec. > 76°C; MS (FAB) $MH^+ 508$; IR (KBr) 3349, 3180, 2932, 2872, 1621, 1531, 1506, 1469, 1296, 948, 838 cm^{-1} ; 1H (NMR) δ 8.20(s, 1H), 8.13(d, 1H, $J = 7.9$ Hz), 7.66(m, 2H), 7.53(br.s., 1H), 7.50-6.60(v.br.s., 1H), 7.19(d, 2H, $J = 8.4$ Hz), 7.09(m, 2H), 6.90(d, 2H, $J = 8.4$ Hz), 6.85(m, 1H), 5.32(s, 2H), 5.01(dd, 1H, $J = 4.3, 8.7$ Hz), 4.18(m, 2H), 3.28(m, 2H), 2.71(t, 2H, $J = 7.2$ Hz), 2.39(m, 1H), 2.25(m, 1H).
- 15

20

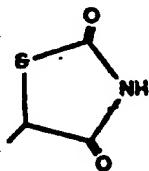
CLAIMS

W claim:

5 1. A compound selected from those of Formula 1:



- 10 wherein the moiety Q is a fused phenyl or fused pyridyl moiety;
 Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;
- Z₂ is hydrogen or a halogen;
- X is hydrogen or oxygen;
- A is C₁-C₆ alkyl, C₁-C₆ alkylaryl or C₁-C₆ alkylheterocyclyl
 wherein aryl is biphenyl, naphthyl or phenyl; and heterocyclyl is a 5 or 6 membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or a sulfur atom; .
- wherein said aryl or heterocyclyl group is optionally substituted with (C₁-C₆)alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C₁-C₄)alkoxy or methylsulfonylamino;
- n is an integer from 0-3;.
- Y is a moiety selected from:
- 25 (a) NHR₁R₂, N⁺R₁R₂R₃;
- (b)
- $\begin{array}{c} \text{NR}_4 \\ \parallel \\ \text{HN} \quad \text{NR}_5 \end{array}$
- (c) CO₂H, CHO;
- (d) CH(R₆)CO₂H, CH(R₆)CO₂CH₃, CH=CHR₇, CH=C(CO₂H)₂;
- 30 (e) a moiety of the formula:



(f) 5-tetrazolyl;

wherein

R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl, or t-

5 butoxycarbonyl

R₄ and R₅ are independently t-butoxycarbonyl or hydrogen or R₄ and R₅
may be joined together to form an imidazoline, imidazolyl or pyrimidine
ring;

R₆ is hydrogen, hydroxy or chloro;

10 R₇ is CO₂H or C(O)NH(CH₂)_pOH wherein p is an integer from 1-4;
and the pharmaceutically acceptable salts, esters and pro-drug forms
thereof.

2. A compound according to claim 1 wherein Q is fused phenyl.

15

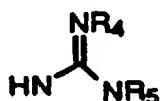
3. A compound according to claim 1 wherein the moiety A is selected from
C₁-C₅ alkyl, CH₂phenyl, CH₂thienyl, CH₂pyridyl, CH₂furyl, and
ethyl piperidine.

20

4. A compound according to claim 1 wherein the moiety Y is selected from:

(a) NHR₁R₂, N⁺R₁R₂R₃;

(b)

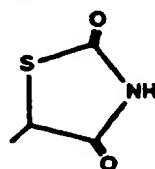


(c) CO₂H;

25

(d) CH(R₆)CO₂H,

(e) a moiety of the formula:



wherein

30 R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl or t-
butoxycarbonyl;

R₄ and R₅ are independently t-butoxycarbonyl or hydrogen; ;

R₆ is hydrogen or hydroxy;

and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

5. A compound according to claim 1 wherein:

5 the moiety Q is a fused phenyl;

Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z₂ is hydrogen or, where Z₁ is a halogen, Z₂ is also a halogen;

X is oxygen;

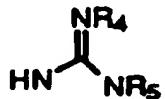
10 A is C₁-C₅ alkyl, CH₂phenyl, CH₂thienyl, CH₂pyridyl, CH₂furyl, or ethyl piperidine; wherein said phenyl, thienyl, pyridyl, furyl or piperidine moiety is optionally substituted with (C₁-C₆)alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl or carbomethoxy;

15 n is an integer from 0-3;

Y is a moiety selected from:

(a) NHR₁R₂, N⁺R₁R₂R₃:

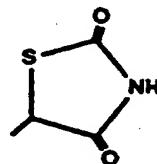
(b)



20 (c) CO₂H;

(d) CH(R₆)CO₂H,

(e) a moiety of the formula:



25 wherein

R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl or t-butoxycarbonyl;

R₄ and R₅ are independently t-butoxycarbonyl or hydrogen;

R₆ is hydrogen or hydroxy;

30 and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

6. The compound according to claim 1, 4-(2-Chlorobenzyl)-2-[2-[4-(guanidinomethyl)phenoxy]ethyl]-3,4-dihydro-3-^xo-2H-1,4-benzoxazine.

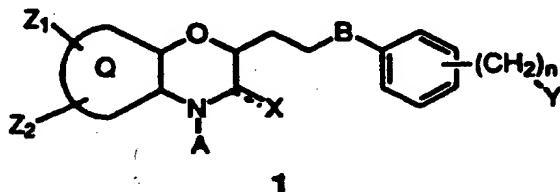
7. The compound according to claim 1, 4-(2-Chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine.
- 5 8. The compound according to claim 1, 4-(3-Chlorobenzyl)-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3,4-dihydro-2H-1,4-benzoxazine.
9. The compound according to claim 1, 4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-pyrido[3,2-b]-1,4-oxazine.
- 10 10. The compound according to claim 1, 2-[2-[4-(2-Aminomethyl)phenoxy]ethyl]-4-(3,5-dichlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine.
- 15 11. The compound according to claim 1, 4-(3,5-Dichlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-3-oxo-2H-1,4-benzoxazine.
12. The compound according to claim 1, 6-Chloro-4-(3-chlorobenzyl)-2-[2-[4-(2-guanidinylethyl)phenoxy]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine.
- 20 13. The compound according to claim 1, 4-(3-Chlorobenzyl)-6,8-dichloro-2-[2-[4-(2-guanidinylethyl)phenoxy]-ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazine
- 25 14. The compound according to claim 1, 4-(3-Chlorobenzyl)-2-[2-[4-(2-guanidinylethyl)phenoxy]-ethyl]-3,4-dihydro-7-methyl-3-oxo-2H-1,4-benzoxazine .
- 30 15. The compound according to claim 1, 2-[2-[3-(2-Aminoethyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazine.
- 35 16. The compound according to claim 1, 4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinylethyl)phenoxy]ethyl]-2H-1,4-benzoxazine .

17. The compound according to claim 1, 2-[2-[4-(3-Aminopropyl)phenoxy]ethyl]-4-(3-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin.
- 5 18. The compound according to claim 1, 4-(3-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(guanidinylmethyl)phenoxy]ethyl]-2H-1,4-benzoxazine.
- 10 19. The compound according to claim 1, 4-(2-Chlorobenzyl)-3,4-dihydro-2-[2-[4-(2-guanidinoethyl)phenoxy]ethyl]-7-nitro-3-oxo-2H-1,4-benzoxazine monohydrochloride.
- 15 20. The compound according to claim 1, 3,4-Dihydro-2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-6-nitro-4-(2-nitrobenzyl)-3-oxo-2H-1,4-benzoxazine.
21. The compound according to claim 1, 5-[4-[2-[4-(3-Chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-2-yl]ethoxy]phenyl]thiazolidine-2,4-dione.
22. The compound according to claim 1, 3,4-Dihydro-4-(2,4-dichlorobenzyl)-2-[2-[4-(2-guanidinoethyl)-phenoxy]ethyl]-3-oxo-2H-1,4-benzoxazine.
23. The compound according to claim 1, 2-[2-[4-(3-Aminopropyl)phenoxy]ethyl]-4-(4-chlorobenzyl)-3,4-dihydro-3-oxo-2H-1,4benzoxazine.
24. A pharmaceutical composition for treating bacterial infections comprising an effective amount of a compound selected from claim 1 in association with a pharmaceutically acceptable carrier.
- 30 25. A method of treating bacterial infections in mammals by administering to a mammal suffering from such infection a therapeutically effective amount of a compound selected from claim 1.
- 35 26. A method of potentiating the activity of an antibacterial agent in mammals by administering said antibacterial agent in combination with a compound selected from claim 1.

27. A pharmaceutical composition for treating bacterial infections comprising an antibacterial agent and a compound selected from claim 1 in therapeutically effective amounts in association with a pharmaceutically acceptable carrier.

5

28. A method of preparing a compound of the formula 1:



10

wherein the moiety Q is a fused phenyl or fused pyridyl moiety;
 Z_1 is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

15

X is hydrogen or oxygen;

A is C₁-C₆ alkyl, C₁-C₆ alkylaryl or C₁-C₆ alkylheterocyclyl

wherein aryl is biphenyl, naphthyl or phenyl; and heterocyclyl is a 5 or 6 membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or a sulfur atom; .

20

wherein said aryl or heterocyclyl group is optionally substituted with (C₁-C₆)alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C₁-C₄)alkoxy or methysulfonylamino;

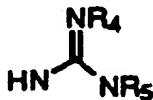
n is an integer from 0-3;.

25

Y is a moiety selected from:

(a) NHR₁R₂, N⁺R₁R₂R₃;

(b)

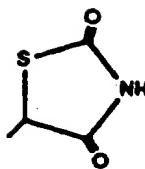


(c) CO₂H, CHO;

30

(d) CH(R₆)CO₂H, CH(R₆)CO₂CH₃, CH=CHR₇, CH=C(CO₂H)₂;

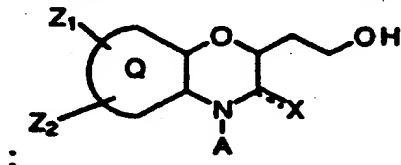
(e) a moiety of the formula:



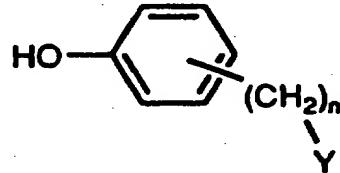
(f) 5-tetrazolyl;

wherein

- 5 R₁, R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl, or t-butoxycarbonyl
R₄ and R₅ are independently t-butoxycarbonyl or hydrogen or R₄ and R₅ may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;
10 R₆ is hydrogen, hydroxy or chloro;
R₇ is CO₂H or C(O)NH(CH₂)_pOH wherein p is an integer from 1-4; and the pharmaceutically acceptable salts, esters and pro-drug forms thereof, which comprises reacting a compound of the formula:

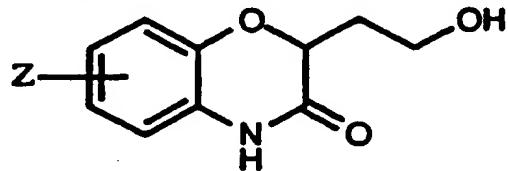


- 15 with a compound of the formula:

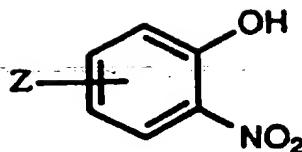


- wherein the moiety Y is protected or unprotected, in a suitable solvent in the presence of an appropriate phosphine and azodicarbonyl reagent, and where
20 Y is protected, removing the protecting group and recovering the compound of formula 1.

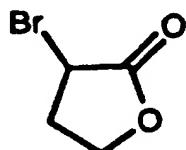
29. A method of preparing a compound of the formula:



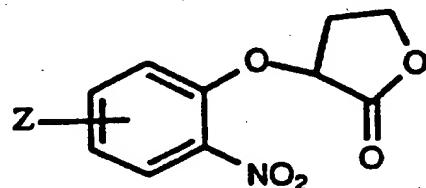
- 25 which comprises reacting a compound of the formula:



with a compound of the formula:

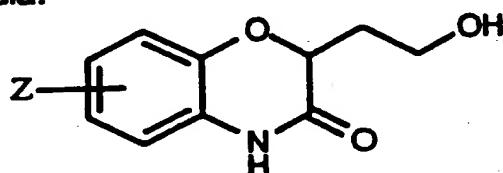


in the presence of a suitable base to yield a compound of the formula:

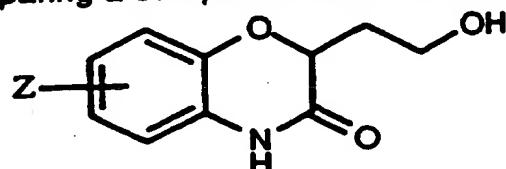


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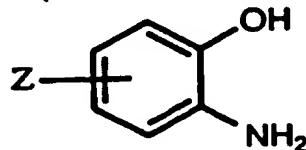
and then cyclizing the compound with an appropriate reducing agent to yield a compound of the formula:



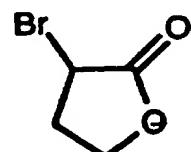
10 30. A method of preparing a compound of the formula:



which comprises reacting a compound of the formula:



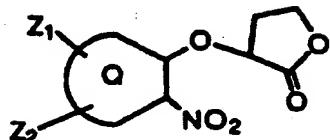
with a compound of the formula:



15

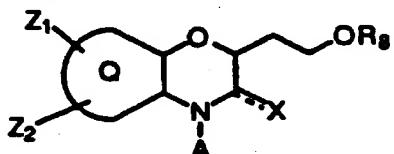
in a suitable base.

31. A compound of the following formula:



wherein the Q moiety is phenyl or pyridyl and Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl; and
 5 Z₂ is hydrogen or a halogen.

32. A compound of the formula:



10 wherein the Q moiety is phenyl or pyridyl and Z₁ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;
 Z₂ is hydrogen or a halogen, A is C₁-C₆ alkylaryl or C₁-C₆
 15 alkylheterocyclyl
 wherein aryl is biphenyl, naphthyl or phenyl; and heterocyclyl is a 5 or 6 membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or a sulfur atom; .
 wherein said aryl or heterocyclyl group is optionally substituted with (C₁-C₆)alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, or amino, carboxyl, carbo(C₁-C₄)alkoxy or methylsulfonylamino; and R₈ is
 20 hydrogen or a hydroxy protecting group.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/US 96/16669

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D265/36 A61K31/535 C07D307/33 C07D413/06 C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 82, no. 23, 9 June 1975 Columbus, Ohio, US; abstract no. 150506b, page 141; XP002020971 see abstract & JP,A,49 125 529 (SANKYO CO., LTD.) 2 December 1974</p> <p>---</p> <p>-/-</p>	1-28

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *'A' document defining the general state of the art which is not considered to be of particular relevance
- *'E' earlier document but published on or after the international filing date
- *'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *'O' document referring to an oral disclosure, use, exhibition or other means
- *'P' document published prior to the international filing date but later than the priority date claimed

- *'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *'Z' document member of the same patent family

1

Date of the actual completion of the international search

12 December 1996

Date of mailing of the international search report

28.01.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 3
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+ 31-70) 340-3016

Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

Intell. Application No
PCT/US 96/16669

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 105, no. 21, 24 November 1986 Columbus, Ohio, US; abstract no. 191020a, M. MOVRIN ET AL.: "1,3-Benzoxazine-2,4-dione and 1,4-benzoxazine-2,3-dione derivatives, as biologically active compounds" page 723; XP002020972 see abstract & ACTA PHARM. JUGOSL., vol. 35, no. 3, 1985, pages 193-202,</p> <p>---</p>	1-28
A	<p>CHEMICAL ABSTRACTS, vol. 107, no. 17, 26 October 1987 Columbus, Ohio, US; abstract no. 154344e, page 704; XP002020973 see abstract & IN,A,158 841 (INDIAN DRUGS AND PHARMACEUTICALS LTD.) 31 January 1987</p> <p>---</p>	1-28
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INTERNATIONAL SEARCH REPORT

Internat'l Application No
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